Genes, chromosomes, and the treatment of bladder cancer

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Disclosures

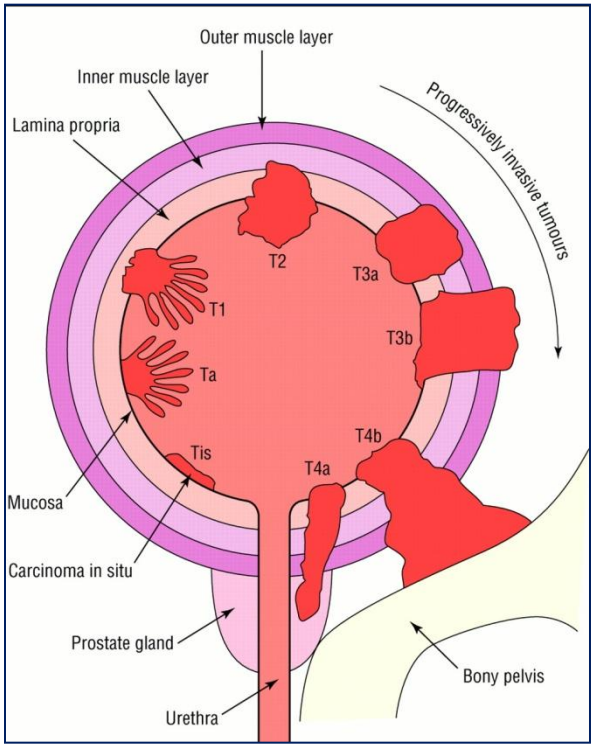
- Consulting
  - Oncogenex
  - Eli Lilly
  - Dendreon
  - Johnson & Johnson

The revolution is here….
But not yet in bladder cancer

- High-throughput genomic technologies have transformed cancer research
- Molecular alterations linked to outcomes in multiple malignancies
  - Predictive: lung, melanoma, breast, CML, colorectal
  - Prognosis: breast, oligodendrogliomas
  - Practice-changing in many malignancies
  - Not yet demonstrated utility in bladder cancer
- Bladder cancer is an attractive target for biomarker discovery and translational science
  - Abundance of resected tissue

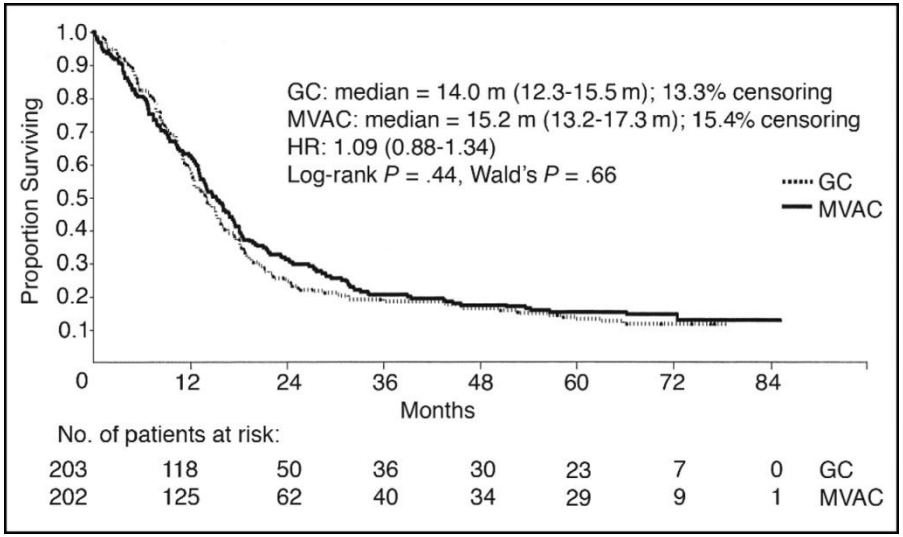
Context: Bladder Cancer 2012

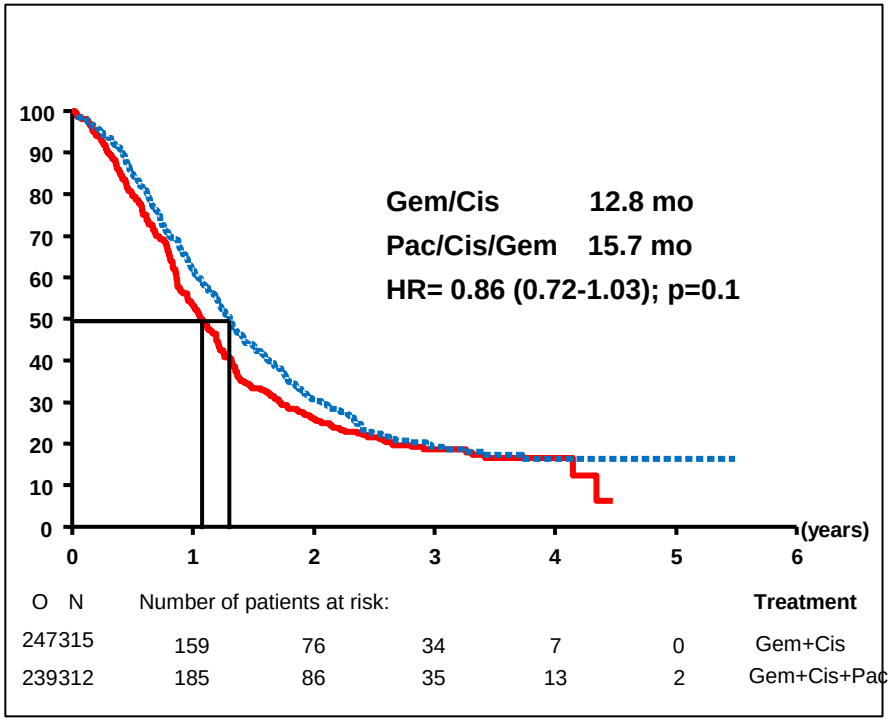
- Non-muscle invasive bladder cancer is most common form
  - 70% present with non-muscle invasive disease
    - 30% will progress to higher stage
  - 30% present with muscle invasive/ metastatic disease
- Prognosis is stage-driven
- Practically:
  - Non-muscle invasive
  - Muscle invasive
  - Metastatic

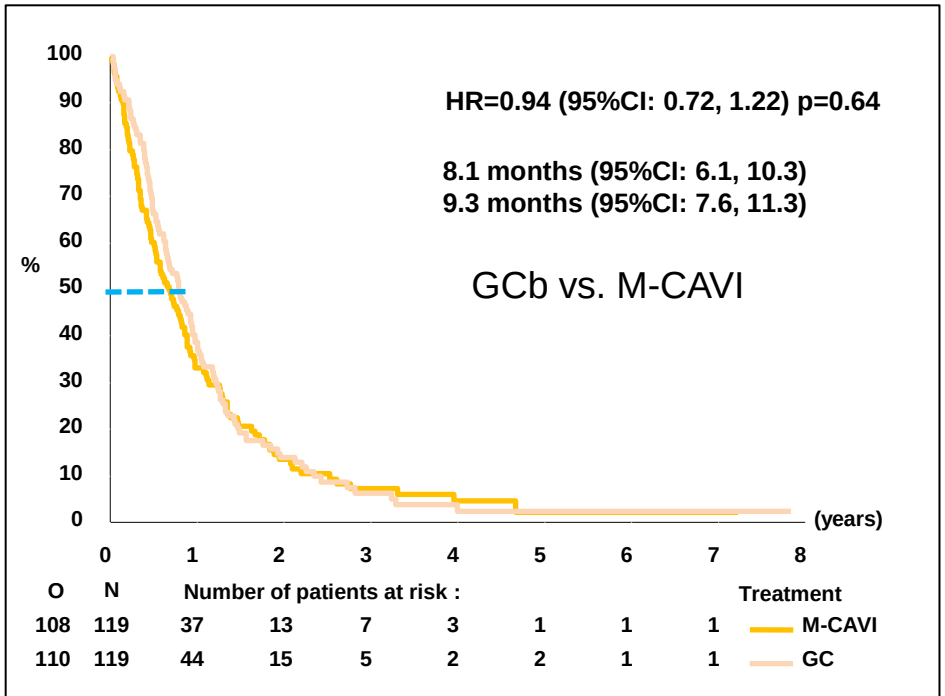


BMJ 1998. 317 : 1366

No major treatment advances in 20 years







www.esmo2012.org

Progress in Urothelial Cancer ?

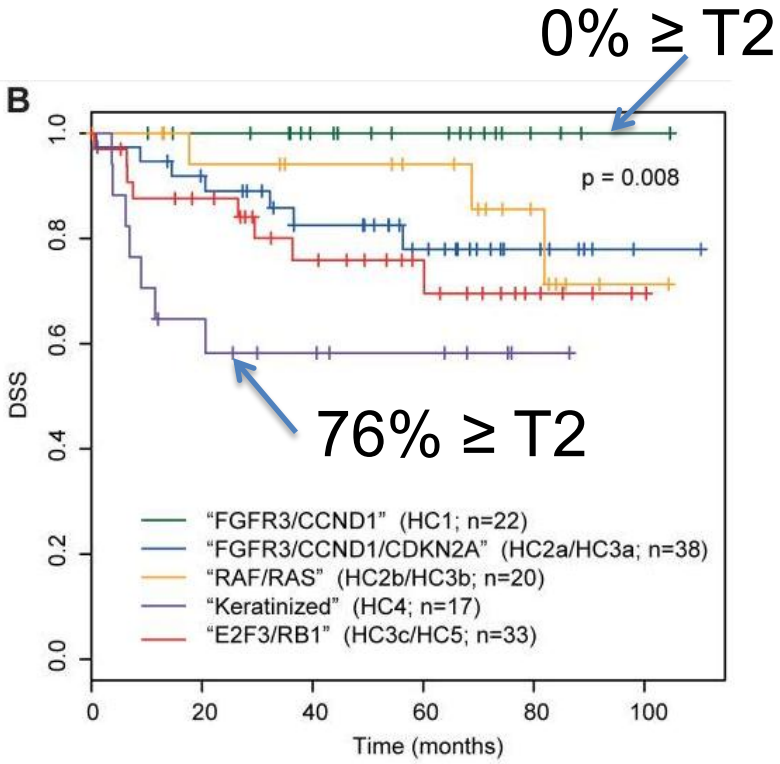
- Newer cytotoxic agents and strategies probably provide little additional benefit
- New strategies are needed
  - Customizing chemotherapy
  - Identification of effective targeted agents
- Novel approaches beyond BCG in NMIBC remain out of reach
- Personalized therapy through predictive markers is crucial but unrealized

Moving beyond therapeutic stagnation in bladder cancer

- Linkage between biological insights and clinical outcomes has not been established
- No validated novel targets
- No validated predictive biomarkers in metastatic disease

Limitations of molecular prognostic studies in UC

- Heterogeneous populations
  - Lump different biology and stages together
- Patients with non-invasive bladder cancer do better
  - Biomarkers found in those patients should predict better survival



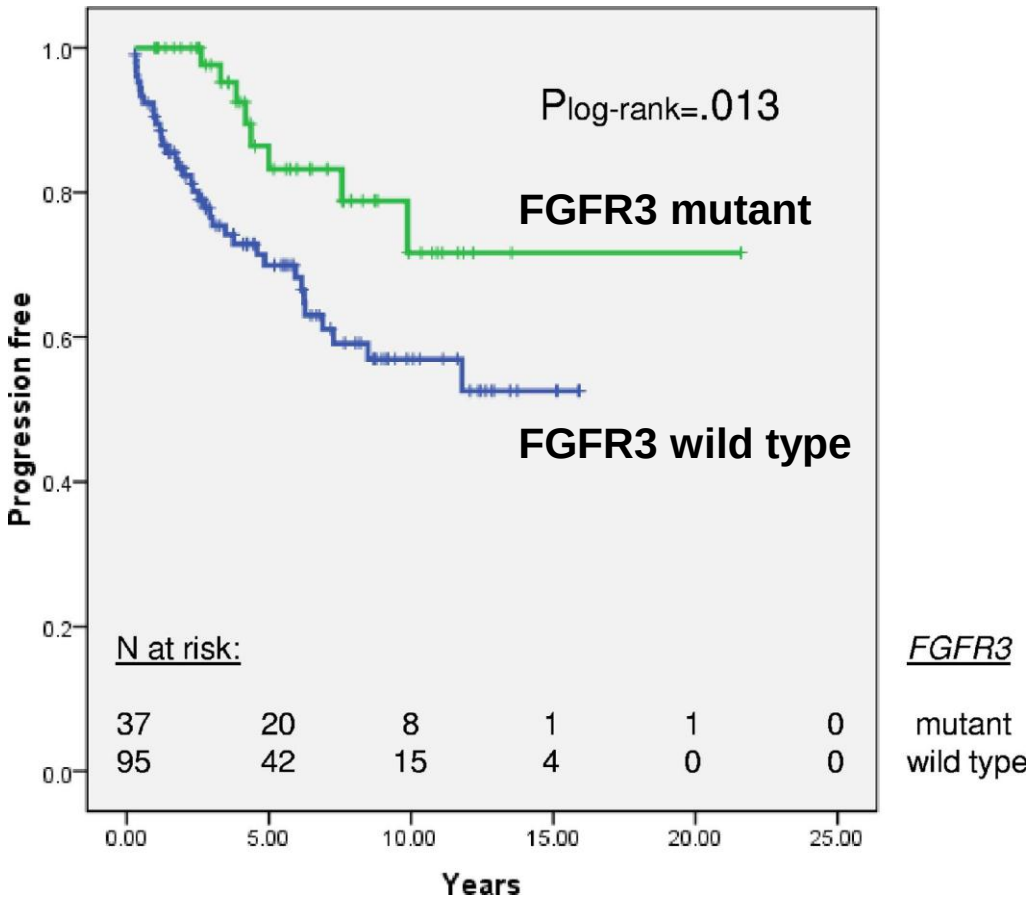
This indicates different biology

But is this more information than the pathology report?

Lindgren et al. PLOS One 2012; 7(6): e38863

Uniform stage leads to relevant clinical outcome data

- Pathologically confirmed pT1 tumors
- FGFR3 activating mutation by SNaPshot
- FGFR3 mutation leads to improved outcomes with pT1 tumors
- Additional validation needed



VIENNA 2012 ESMO congress

www.esmo2012.org

Van Rhijn, et al. J Urol 2012

Rethinking biomarker studies in UC

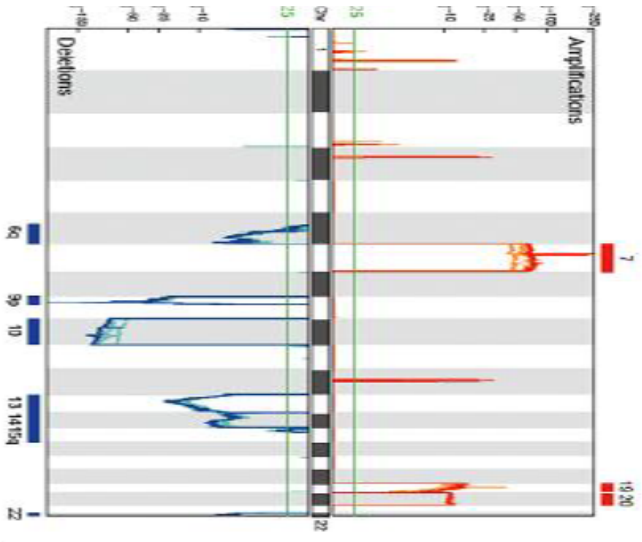
- Uniform cohorts are needed
- Patients in biomarker studies should have similar disease states and outcomes be determined from consistent time points

Bladder cancer genome

- Characterized by many recurrent genomic changes
  - Target rich environment
  - Many different druggable alterations

Methodologies to analyze the genome

COPY NUMBER

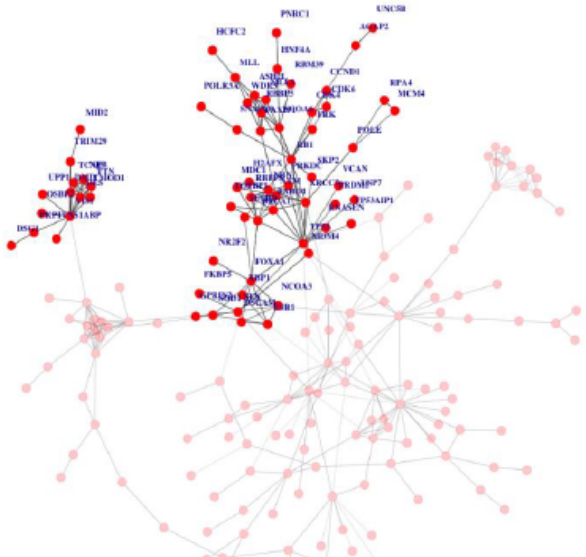


GISTIC 1.0
Beroukhim et al. PNAS (2007)
GISTIC 2.0
Mermel et al. Genome Biol. (2011)

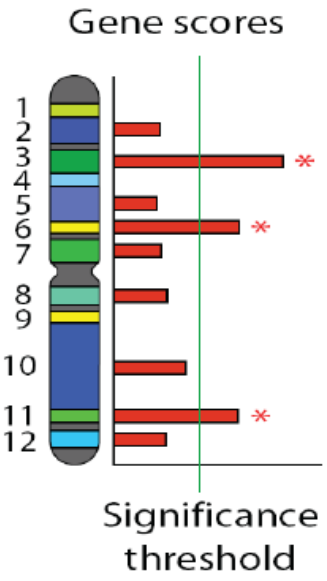
Uses: Frequency and amplitude of events
Separates broad and focal gains and losses

ALL MODALITIES

NetSig (in development)
Zou et al., in development
Uses: all types of alterations to identify clusters of mutated genes in protein-protein networks



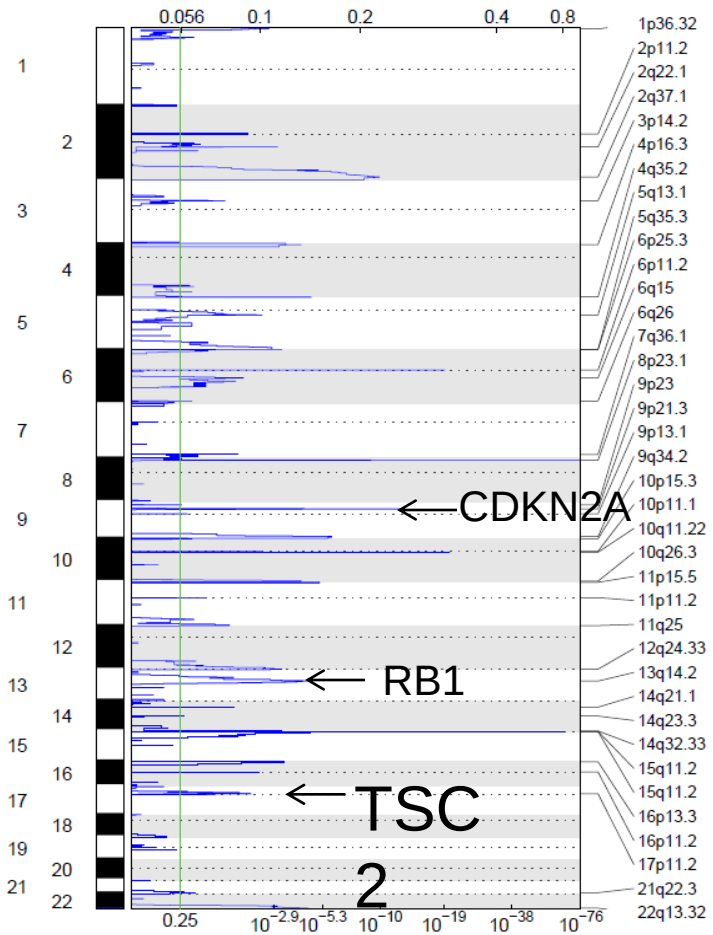
MUTATIONS

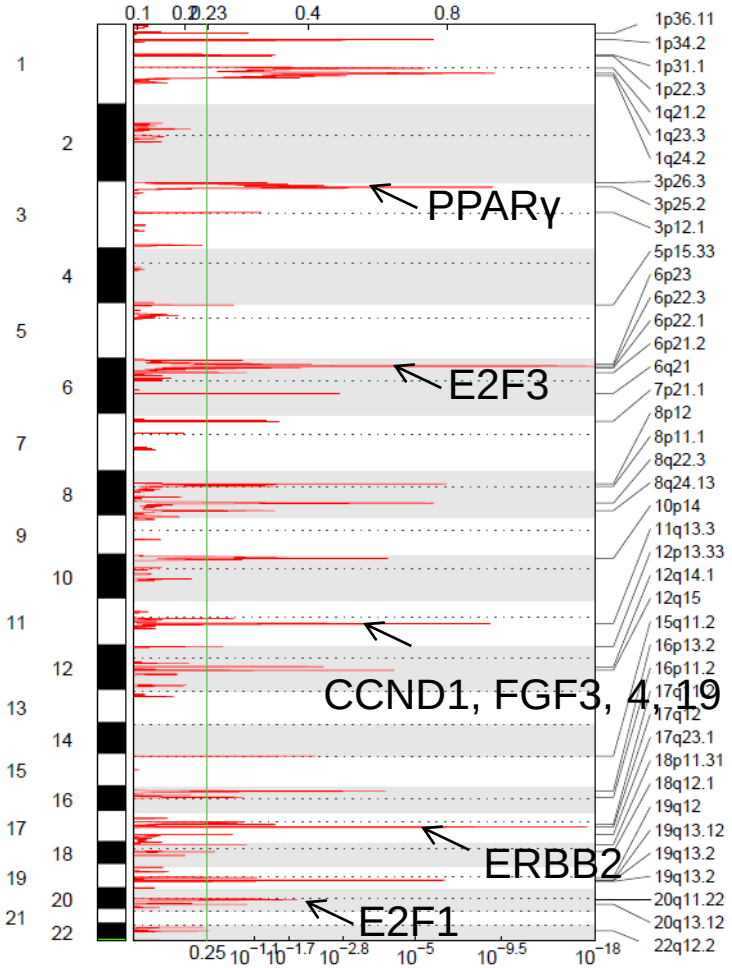


MutSig
Lawrence et al. in development
Getz et al. Science (2007)
Uses: Number and types of mutations; corrects BMR for expression, gene footprint size etc.
Works on genes, genesets and conserved regions (intervals on the genome)

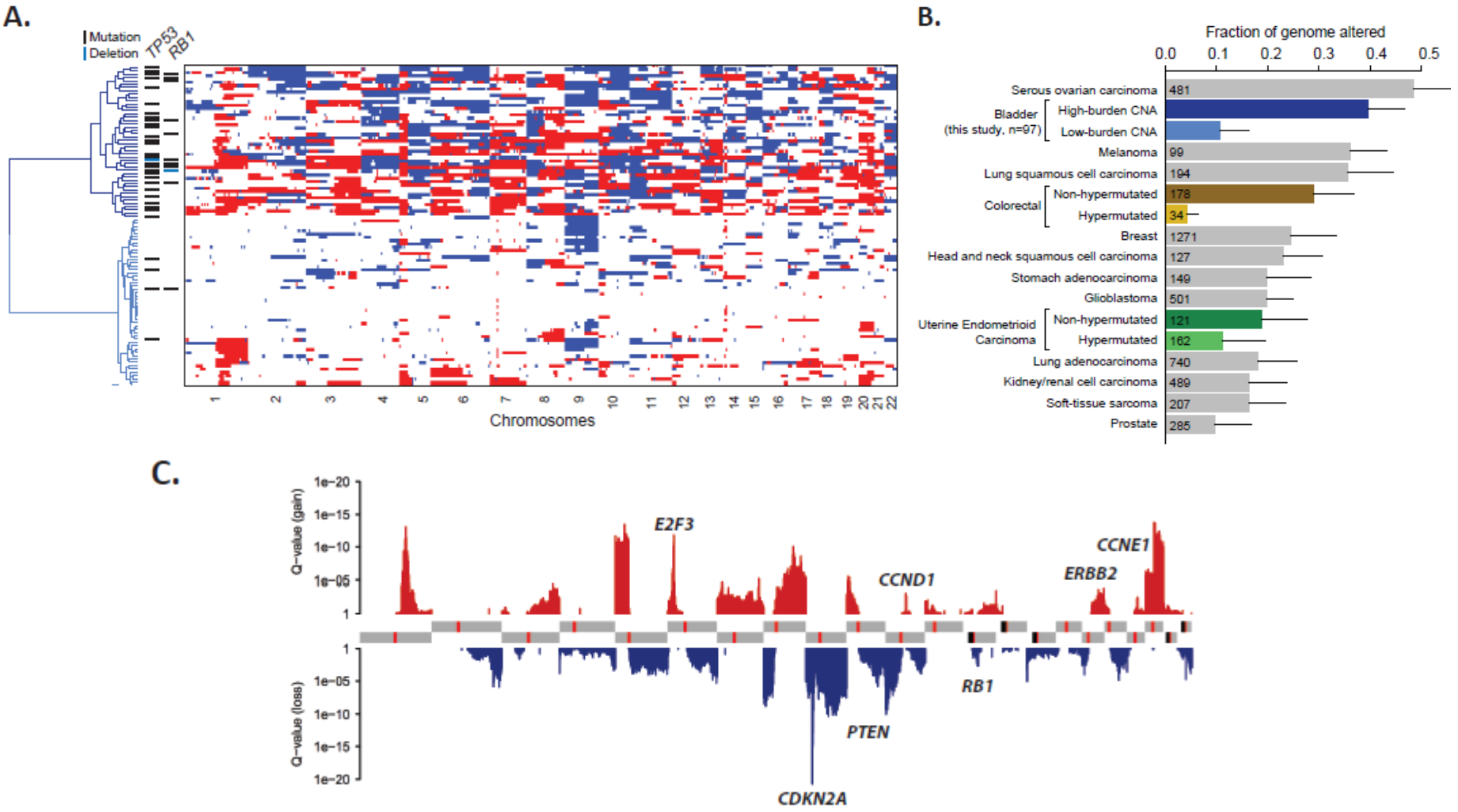
Craig Mermel, Rameen Beroukhim, Steve Schumacher, Mike Lawrence, Lihua Zou, Alex Ramos, Gregory Kryukov, Petar Stojanov

Map of recurrent gains and losses in primary tumors of patients with metastases

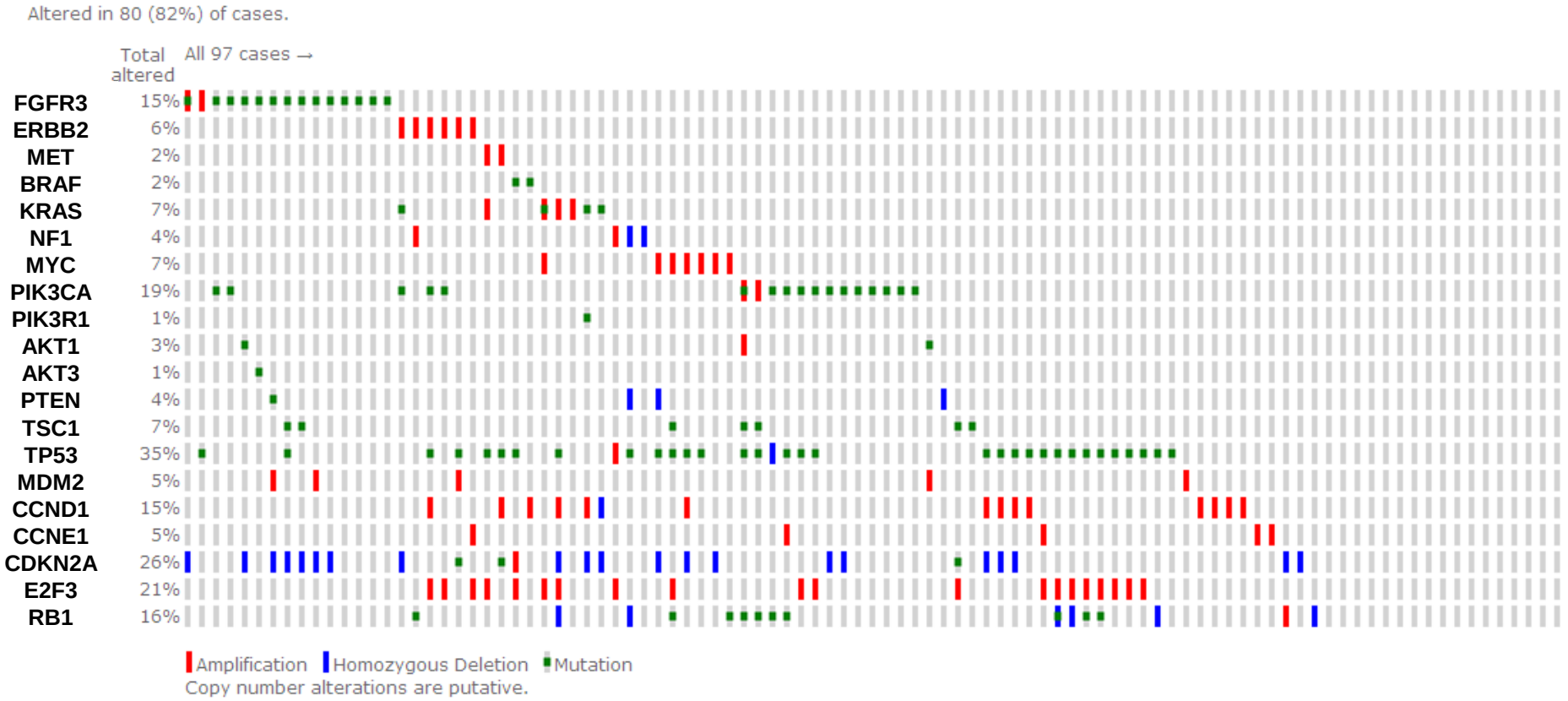




Landscape of Copy Number Alterations in High-Grade Bladder Cancer

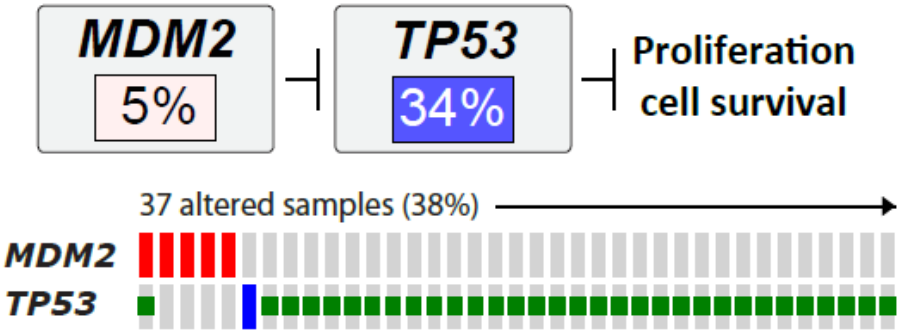


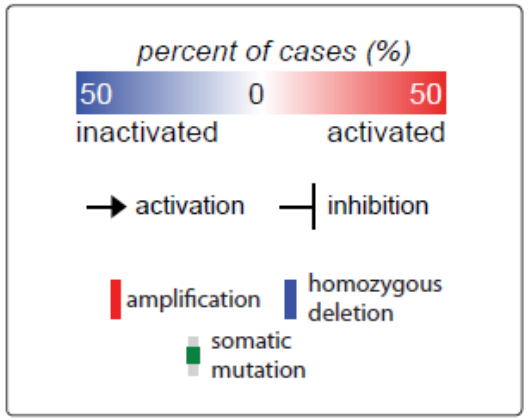
Copy number and mutation analysis reveals some mutual exclusivity between different genomic alterations in UC



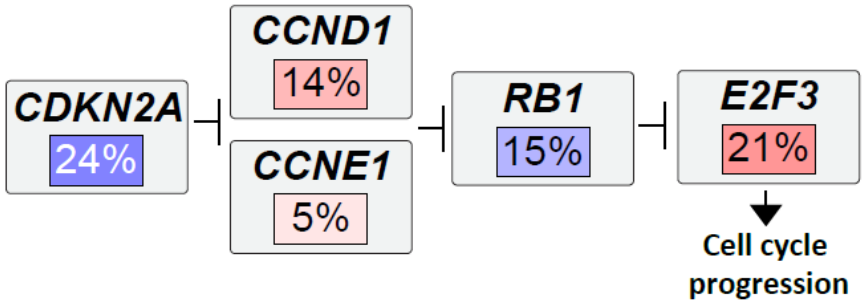
Composite heatmap of copy number alterations and mutations within 97 HGUC tumor samples

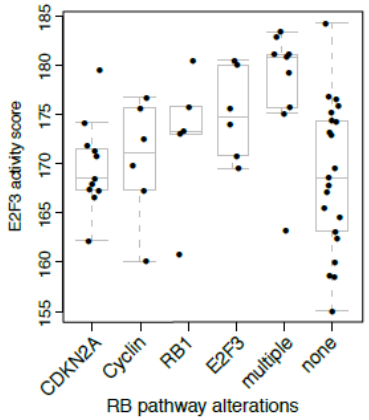
A. P53 signaling

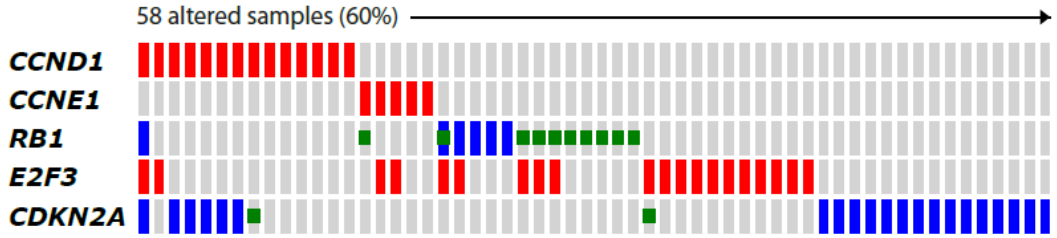




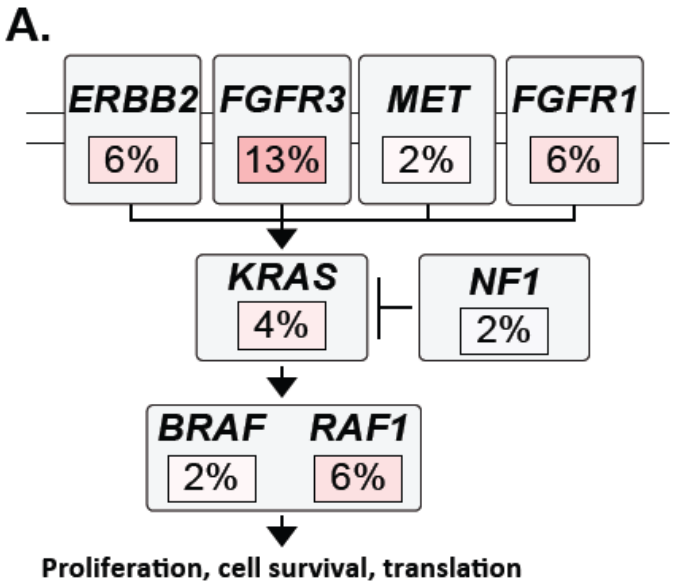
B. RB signaling

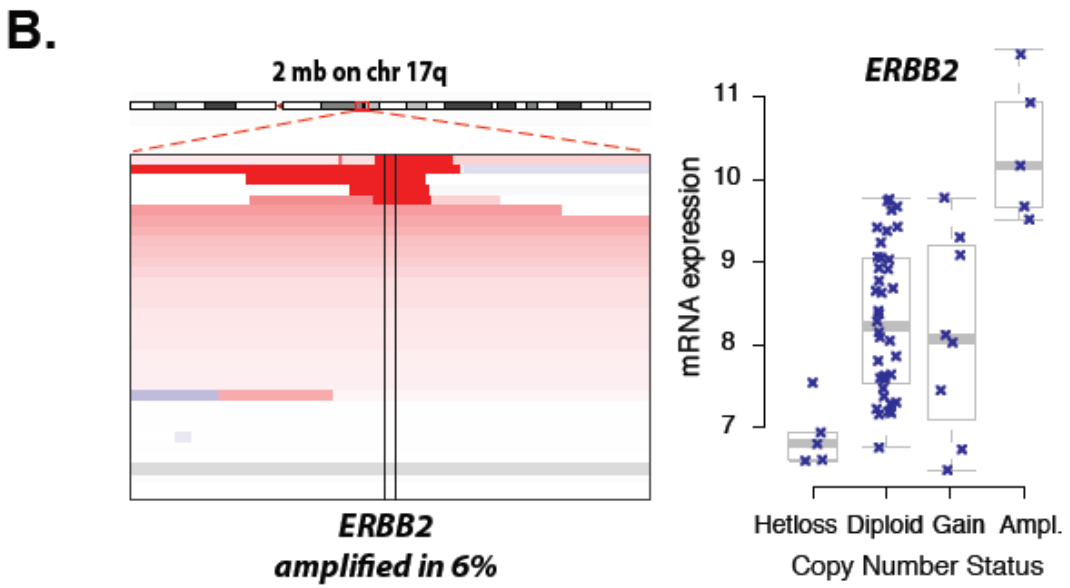


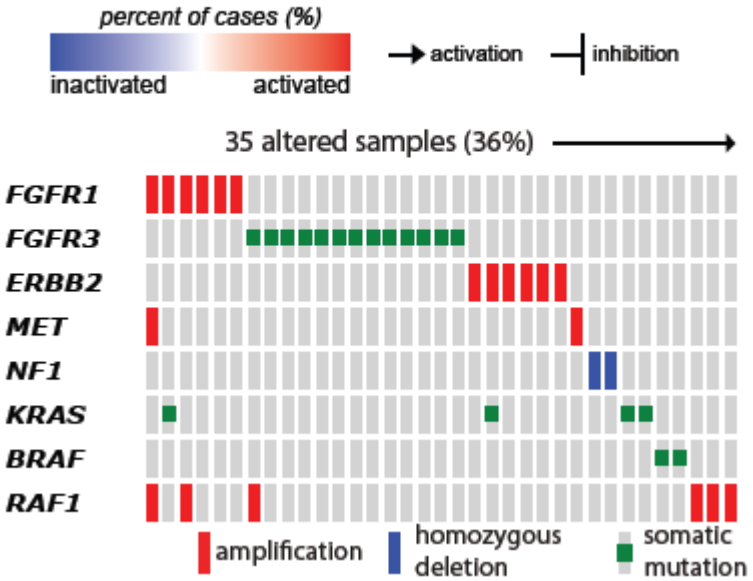


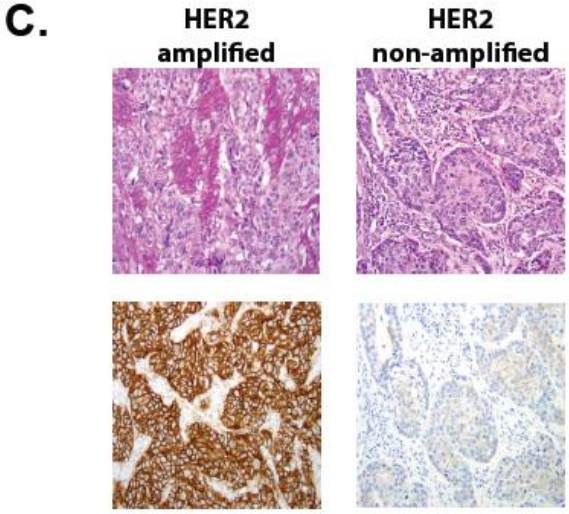


Multiple oncogenic pathways altered



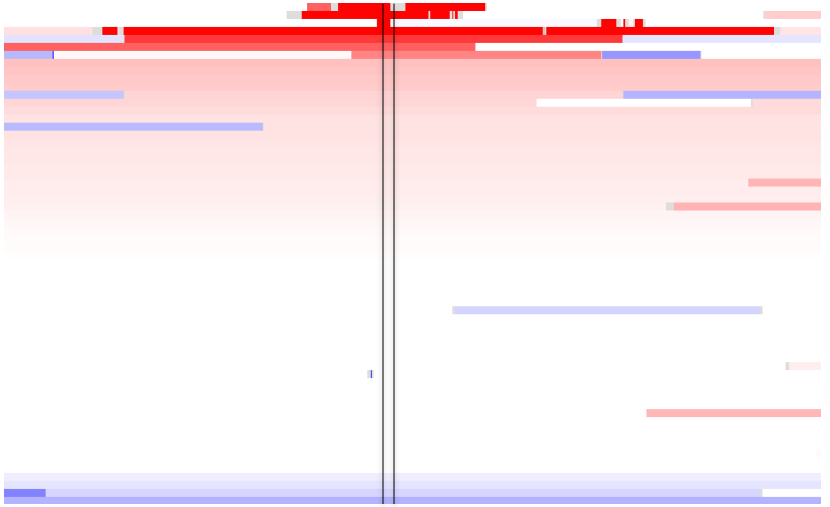






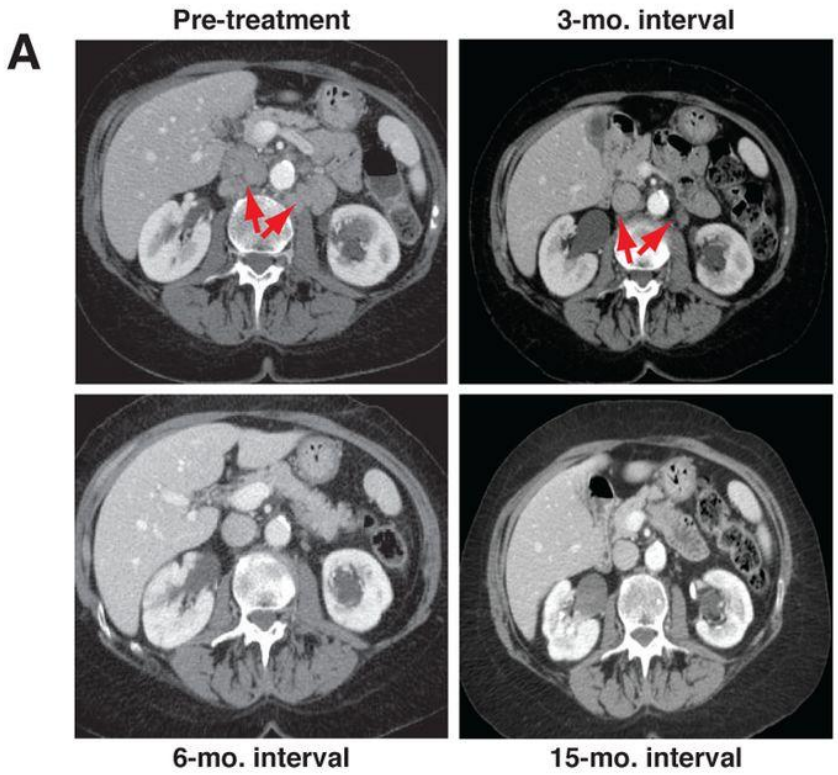
ERBB2 Incidence 6-11% by Copy Number Analysis

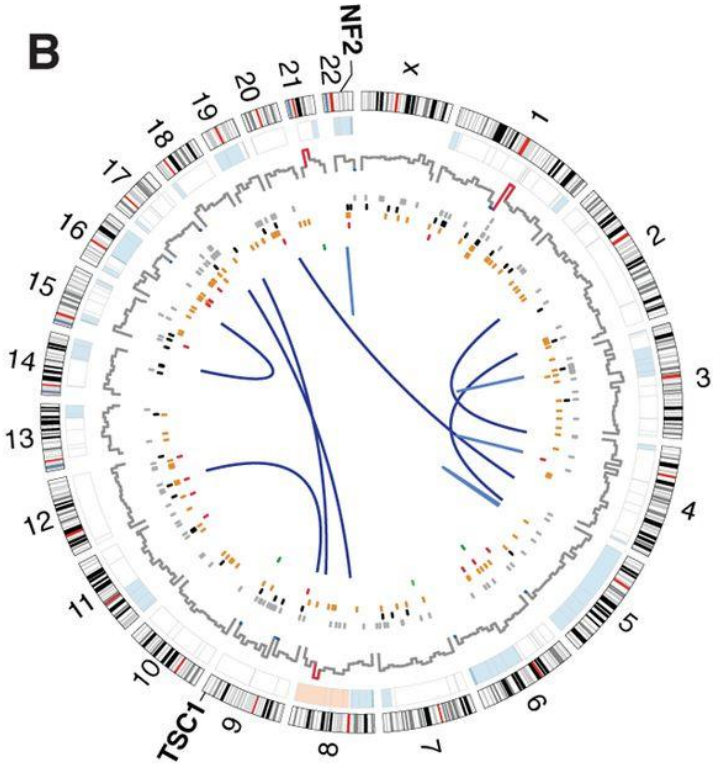
Spain

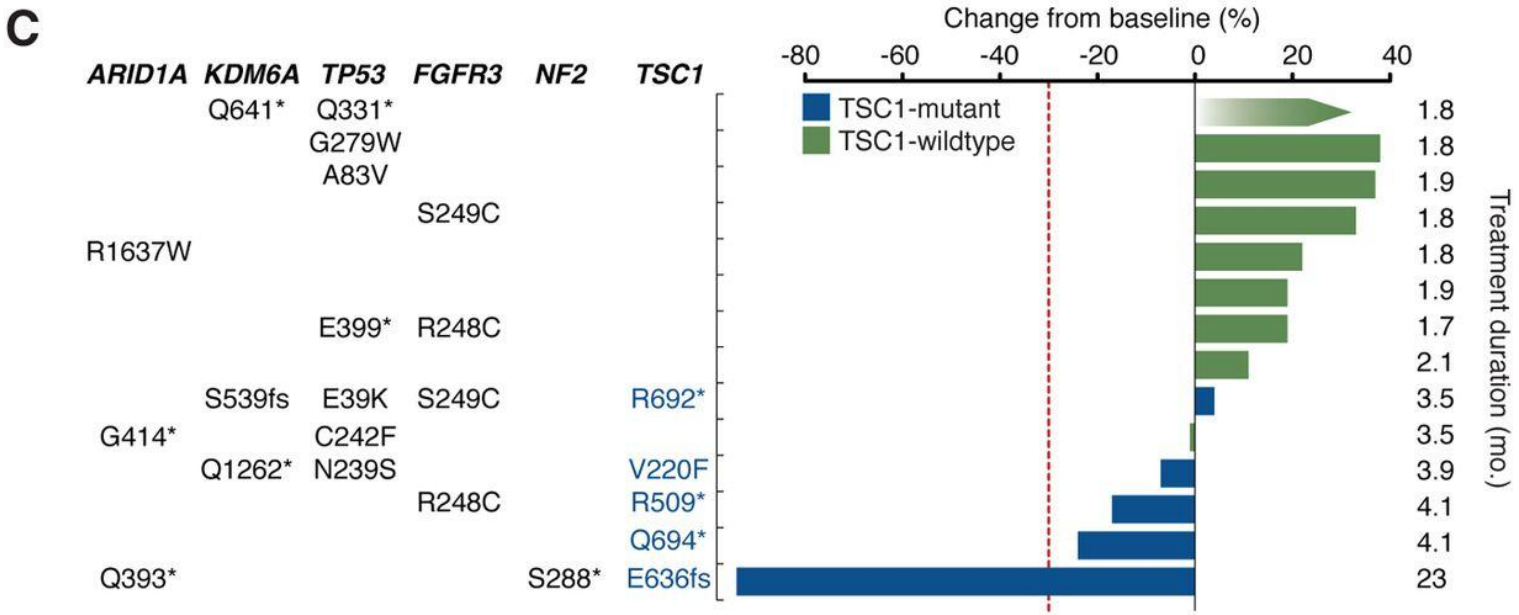


DFCI

Genetic basis of extreme everolimus sensitivity



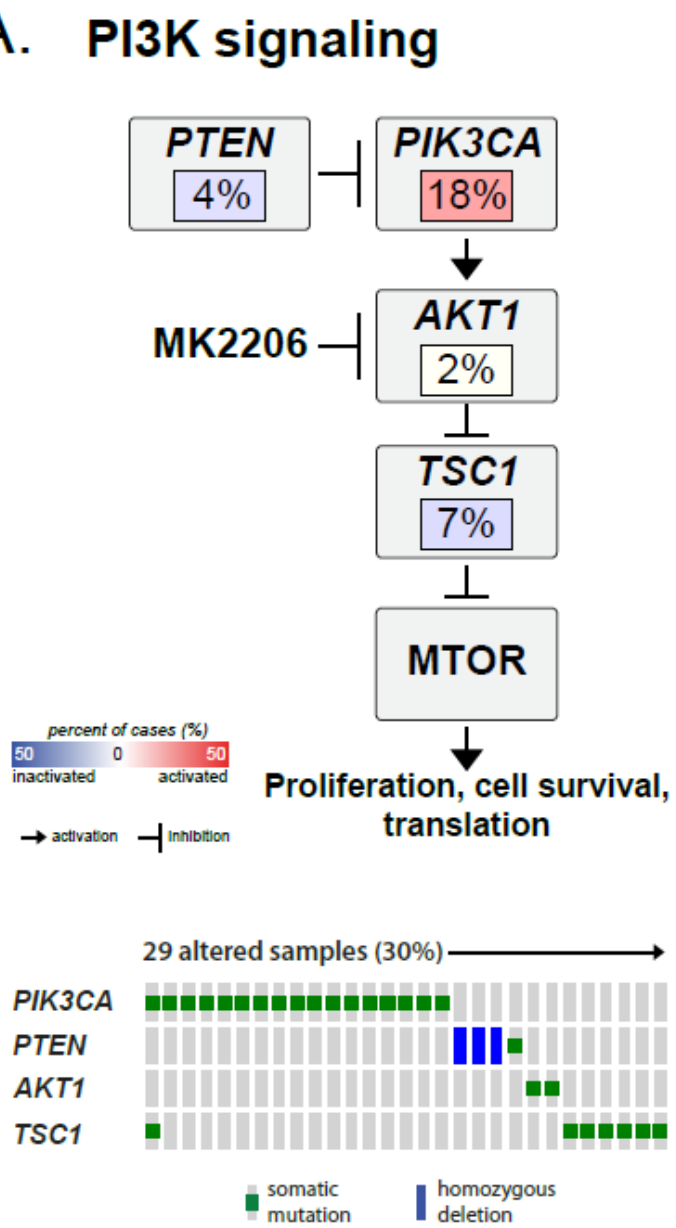




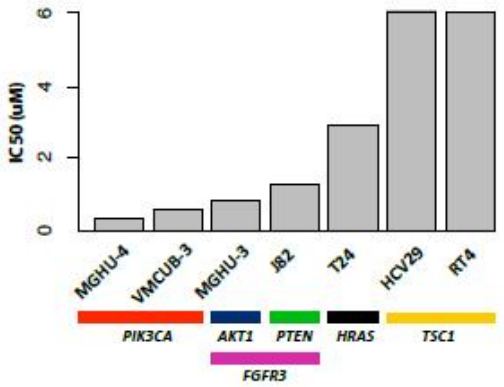
Iyer, et al, *Science* 2012

PI3K/Akt pathway mutations confer sensitivity to Akt inhibition in high-grade UC cell lines

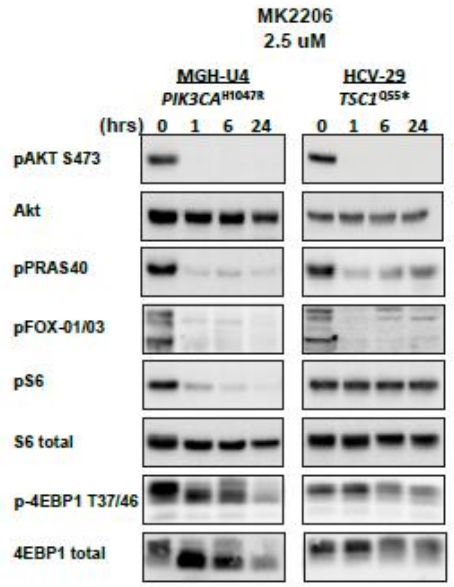
A.



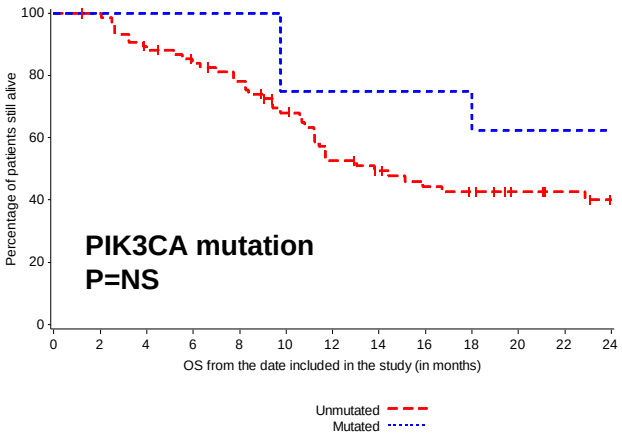
B.

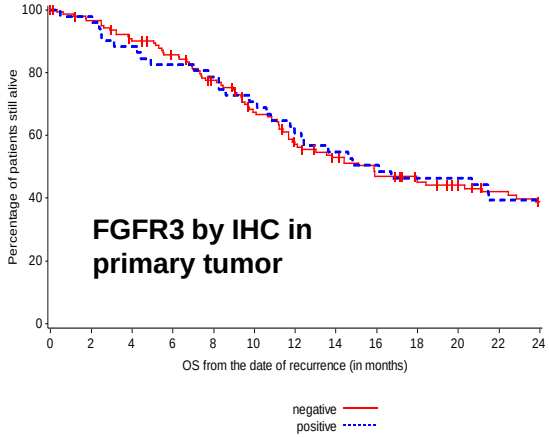


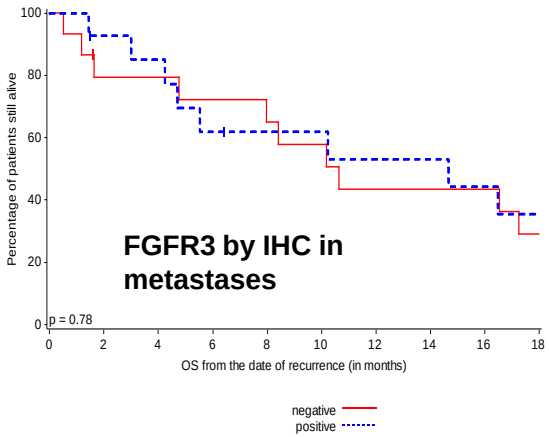
C.

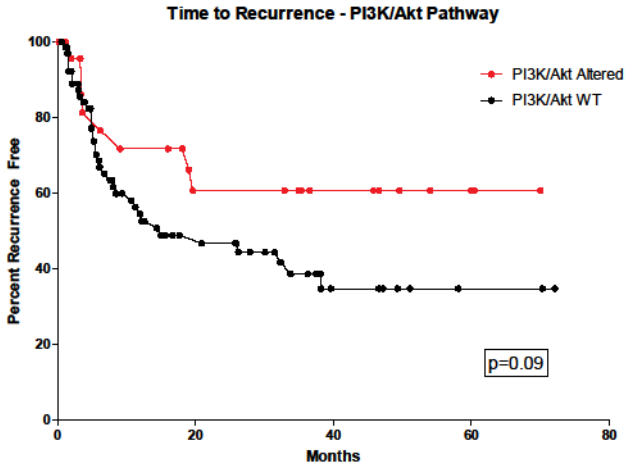


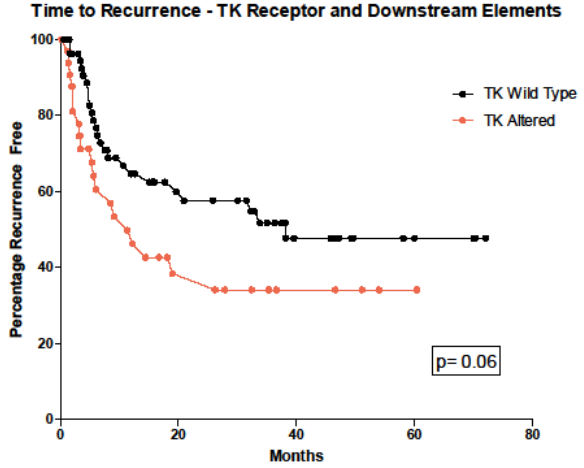
Molecular targets and outcomes





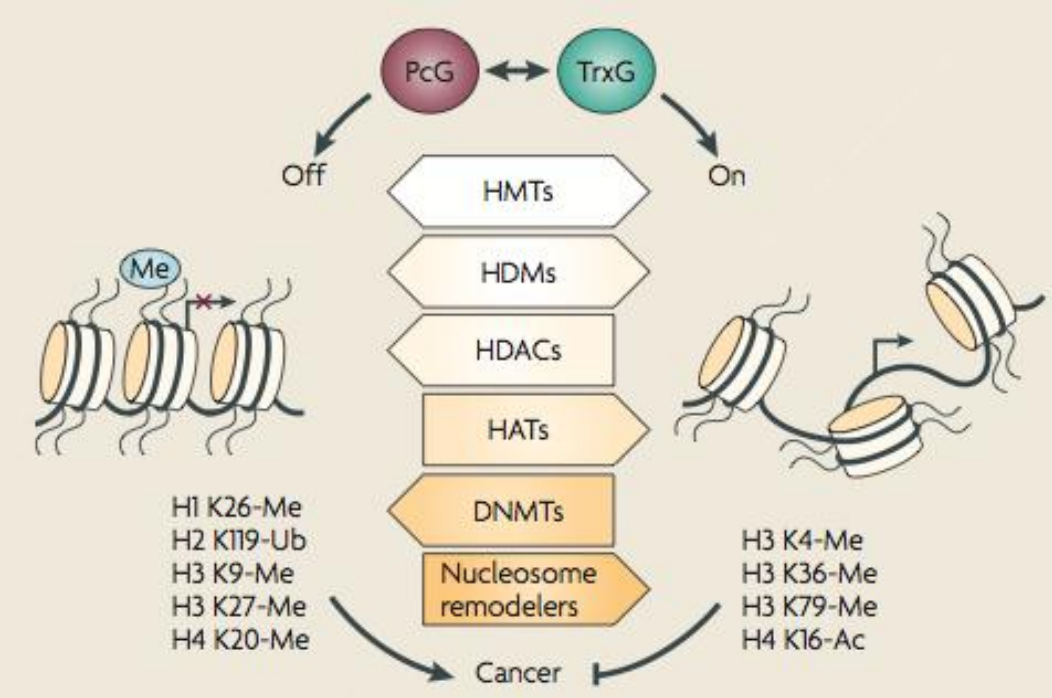






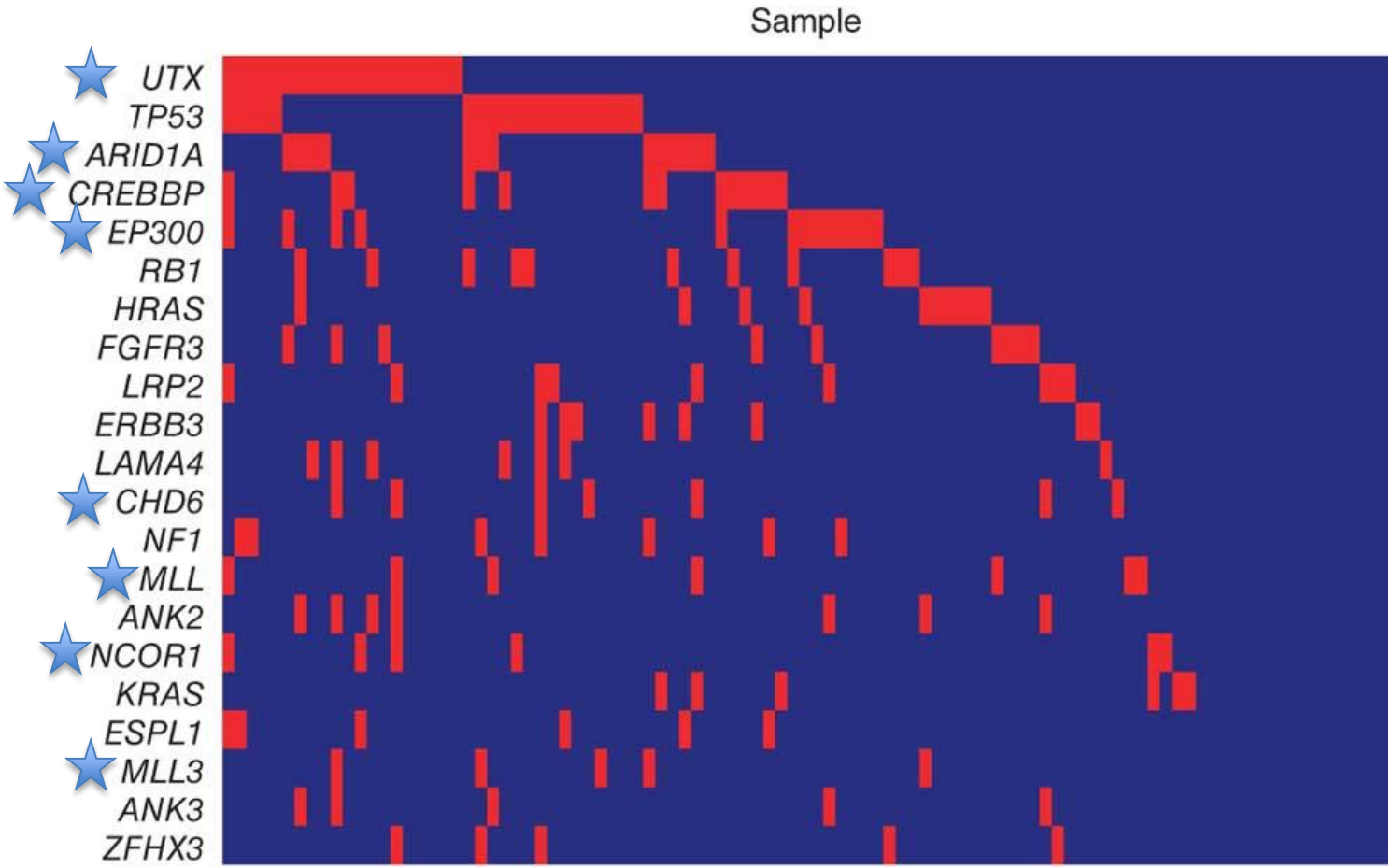
Chromatin-modifying genes

- Methylation of DNA leads to conformational and structural changes
  - Histone deacetylation and changes in chromatin structure
- Altered methylation changes gene expression in cancer cells
  - Global hypomethylation
  - Focal hypermethylation
- Recently described in bladder cancer



Mills, et al, *Nature Reviews Cancer* 2010

Chromatin remodeling genes identified in UC:
Most mutations are predicted to be inactivating

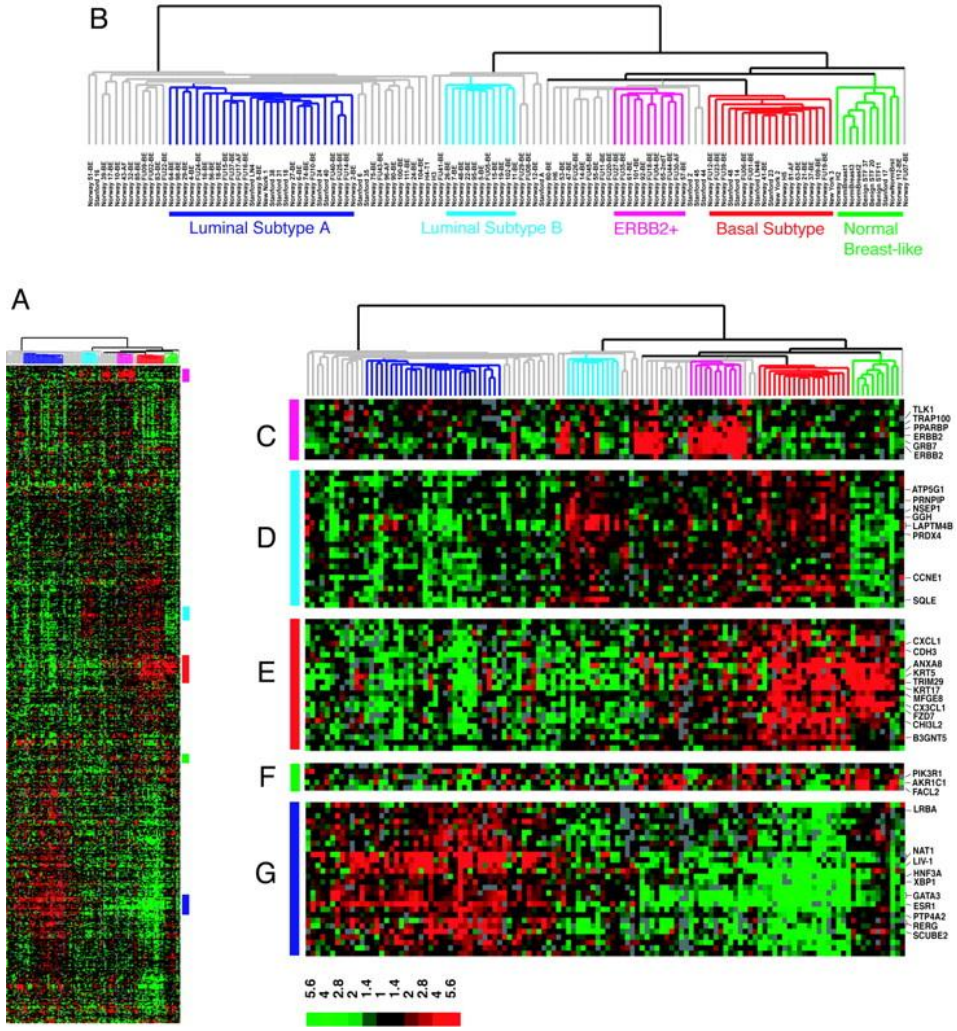


Gui, et al. Nature Genetics 2011

Clinical relevance and utility of CMG mutation unclear

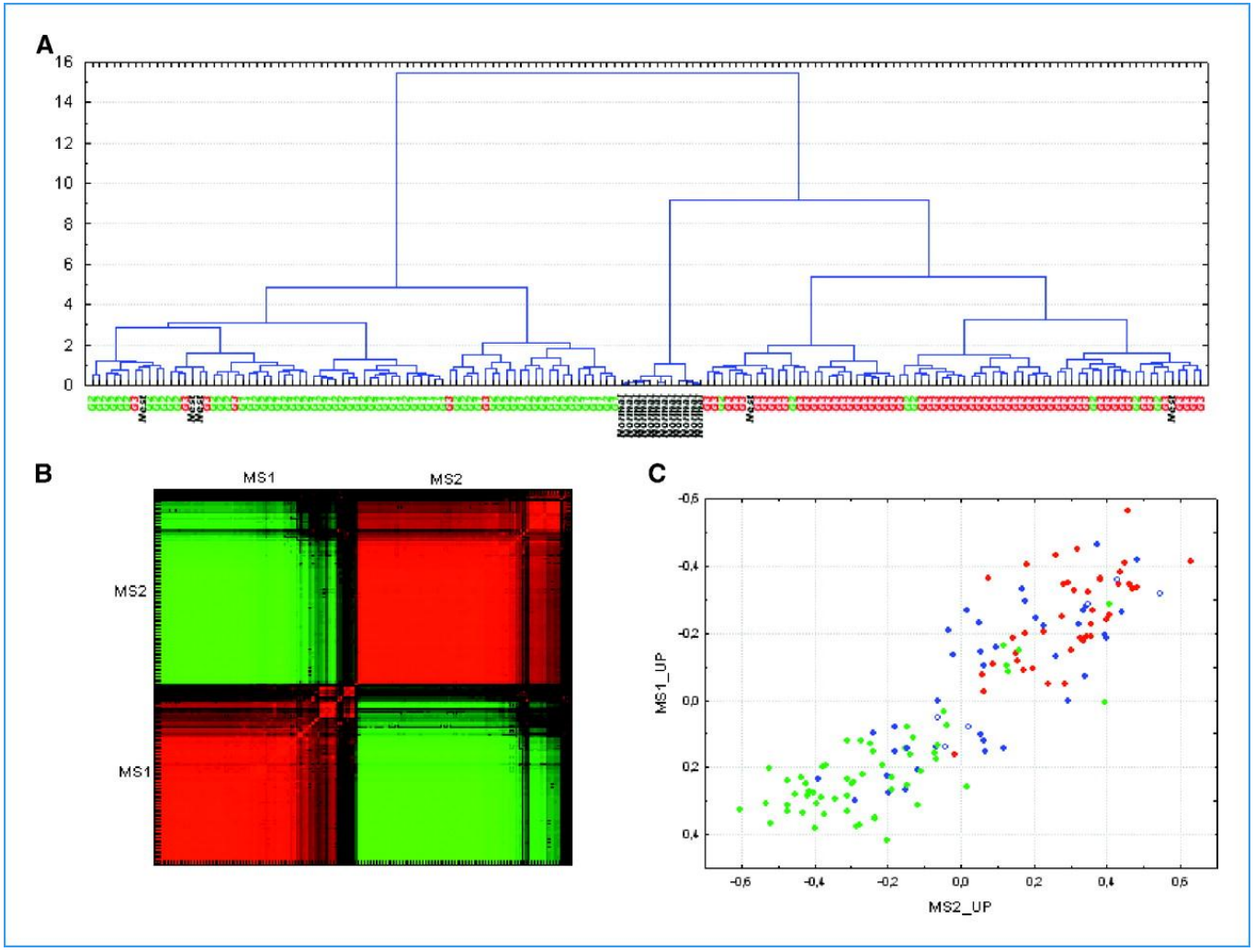
- Linkage of genotype to clinical phenotype is not clearly present
- Therapeutic implications not yet clear
  - Not easily druggable

mRNA expression: Hierarchical clustering in breast cancer defines subtypes with clinical biology



Sørlie T et al. PNAS 2003;100:8418-8423

Bladder cancer: mRNA expression yields 2 intrinsic classes of tumors



Panel A

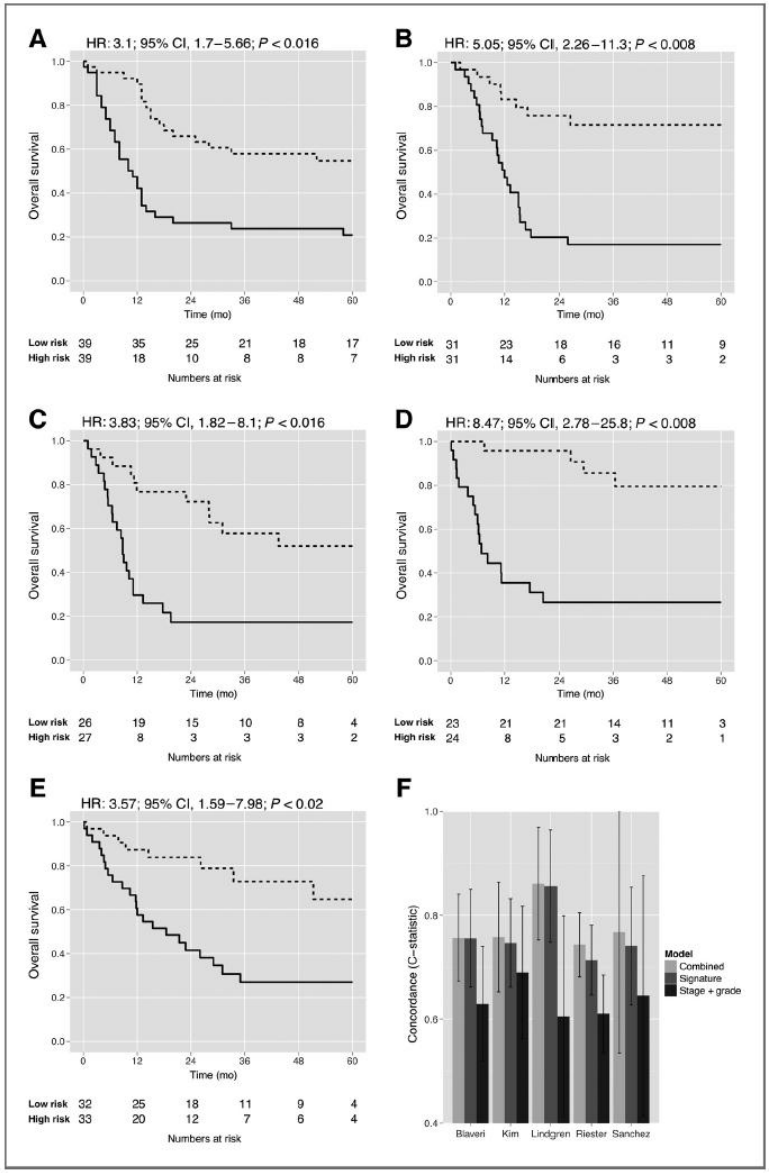
- Green: low grade (g1/2)
- Red: high grade (g3)

- mRNA expression recapitulates morphology
- Gives little insight into prognosis of the tumor

Lindgren D et al. Cancer Res 2010;70:3463-3472

“Meta-analysis” of multiple profiling datasets

Gene symbol	Gene name
APOBEC3B	Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B
ATF3	Activating transcription factor 3
CCL5	Chemokine (C–C motif) ligand 5
DGCR2	DiGeorge syndrome critical region gene 2
ENDOD1	Endonuclease domain containing 1
FADD	Fas (TNFRSF6) associated via death domain
JUNB	Ribonuclease H2, subunit A
LMO7	LIM domain 7
MAP2K1	Mitogen-activated protein kinase kinase 1
MAP3K1	mitogen-activated protein kinase kinase kinase 1
PDGFC	Platelet-derived growth factor C
PEA15	Phosphoprotein enriched in astrocytes 15
PFN1	Perforin 1 (pore-forming protein)
PPP1R12A	Protein phosphatase 1, regulatory (inhibitor) subunit 12A
PRDX1	Peroxiredoxin 1
PRMT1	Protein arginine methyltransferase 1
SLC1A5	Solute carrier family 1 (neutral amino acid transporter), member 5
TNFAIP6	TNF, α-induced protein 6
TSG101	Tumor susceptibility gene 101
TSPAN5	Tetraspanin 5



Riester, et al. Clin Cancer Res. 2012 Jan 6.

mRNA expression profiling

- mRNA expression profiling has identified distinct groups of tumors
- Findings associate with clinical features
- Can lead to more accurate risk stratification
- Therapeutic implications are unclear
  - MammaPrint, OncotypeDX are still not ready in bladder cancer

Translating findings to clinical practice

- No single druggable alteration characterizes the majority of tumors
  - Low mutation frequencies of multiple genes
- Potential model system for targeted therapy
  - None yet proven
- Requires trials enriched for patients to demonstrate proof of concept

Translating genomic information to bladder cancer practice

- Pre-screening patients for relevant molecular alterations
- Potentially relevant pathways
  - ERBB2
  - PIK3CA/mTOR/PTEN/AKT
  - CDK4/CCND1
  - FGFR3
  - BRAF
- Designing trials to demonstrate clinical benefit

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Martin Voss MD
Philip Kim, M.D.
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Matthew Milowsky, MD

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Jaegil Kim PhD
Gad Getz PhD

Most mutations are predicted to be inactivating