

Supplemental Figure Legends

Supplemental Figure 1. Composition of human tissue microarray (TMA).

Supplemental Figure 2. *K-ras* activation is sufficient to drive the RAS/MAPK pathway but is not sufficient to initiate cancer. A, Control (*WT*) and *C⁺;K-ras^{LW}* prostates showing P-MAPK and P-AKT expression. Low mag bar = 150 μ m, high mag bar = 50 μ m. B, *Pten^{-/-};Kras^{G12D}* cells were isolated from *C⁺;Pten^{L/L};K-ras^{LW}* mutant prostates, infected with GFP-lenti virus and injected to the tibia of *NOD;SCID;IL2r γ -null* recipients.

Supplemental Figure 3. AR signaling is repressed in *C⁺;Pten^{L/L};K-ras^{LW}* mutants. A, AR expression in control (*WT*), *C⁺;K-ras^{LW}*, *C⁺;Pten^{L/L}* and *C⁺;Pten^{L/L};K-ras^{LW}* (primary and lung metastasis), low mag bar = 150 μ m, high mag bar = 50 μ m. B, Effect of K-ras activation on AR gene expression as evaluated by Gene Set Enrichment Analysis (GSEA) comparing *C⁺;Pten^{L/L}* and *C⁺;Pten^{L/L};K-ras^{LW}* mutants, as exemplified in, C, by the reduction of the AR target genes *Mme*, *Msmb* and *Nkx3.1* in *C⁺;Pten^{L/L};K-ras^{LW}* mutants..

Supplemental Figure 4. *C⁺;Pten^{L/WT};K-ras^{LW}* mutants progress to invasive and poorly differentiated carcinoma correlating with PTEN loss. A, Histology of *C⁺;Pten^{L/WT};K-ras^{LW}* mutant prostates at 10, 20 and 30 wks. B, P-AKT and Ki67 expression in *C⁺;Pten^{L/WT};K-ras^{LW}* mutants at 10 wks and C, PTEN loss and P-AKT expression in *C⁺;Pten^{L/L}* and *C⁺;Pten^{L/WT};K-ras^{LW}* mutants (40 wks). Low mag bar = 150 μ m, high mag bar = 50 μ m.

Supplemental Figure 5. A, p63 expression in human and murine (*C⁺;Pten^{L/L};K-ras^{LW}*) prostate cancer progression, bar = 50 μ m. B, p53 and p27 expression in *C⁺;Pten^{L/L}* and *C⁺;Pten^{L/L};K-ras^{LW}* mutants (10 wks), low mag bar = 150 μ m, high mag bar = 50 μ m. C, N-cadherin and synaptophysin expression in *C⁺;Pten^{L/L};K-ras^{LW}* mutants (10 wks), bar = 50 μ m.

Supplemental Figure 6. A, Heat maps comparing the overlap of differentially expressed genes in human metastatic tumors (metastasis – primary; y-axis) and in murine *Pb-Cre⁺;Pten^{L/L};K-ras^{LW}* mutants (*Pten;Kras* – *Pten* null; x-axis) based on rank-rank hypergeometric overlap (RRHO) analysis used to measure and visualize the degree of statistically significant overlap between two expression signatures. The color bar indicates the transformed \log_{10} hypergeometric enrichment p-value between two signature gene sets. The high heat areas on

bottom left and top right corners indicate the significant overlap between differentially expressed genes in *Pb-Cre⁺;Pten^{L/L};K-ras^{L/W}* mutants and human metastatic tumors. *B*, corresponding examples of repressed and elevated genes (lower panel).

Supplemental Figure 7. Genotyping of isolated stem/progenitor cells and resulting metastatic lesions. *A*, Genotyping of passage 3 spheres derived from *C⁺;Pten^{L/L};K-ras^{L/W}* mutants. *B*, Genotyping of FACS sorted primary cells from *C⁺;Pten^{L/L};K-ras^{L/W}* mutants. *C*, Genotyping of metastatic lesions resulting from transplantation of primary, FACS sorted cells from *C⁺;Pten^{L/L};K-ras^{L/W}* mutants.

Gleason Graded TMA-2009

Pathology	# Patients	# Cores	Treatment
BPH/PIN	23	46	None
Gleason 6-7	35	70	None
Gleason 7-8	24	48	None
Gleason 9-10	6	12	None
Total	88	176	

NHT TMA-2009

Pathology	# Patients	# Cores	Treatment
G3	7	14	None
G4	3	6	None
G5	4	8	None
TR Pattern	5	10	1 M
TR Pattern	3	6	1.5 M
TR Pattern	3	6	2 M
TR Pattern	5	10	3 M
TR Pattern	8	16	5-6 M
TR Pattern	18	36	7-8 M
TR Pattern	16	32	9-12 M
TR Pattern	16	32	CRPC
Total	88	176	

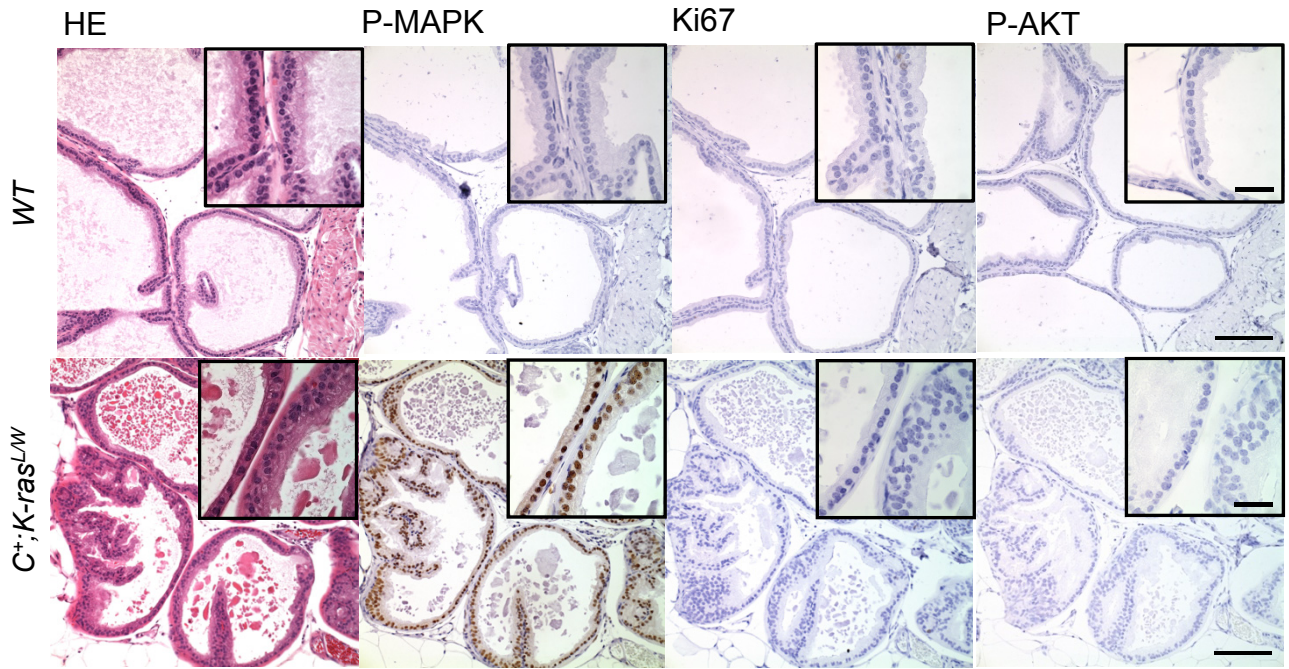
CRPC/TURP-2009

Pathology	# Patients	# Cores	Treatment
CRPC	12	24	N/A
Benign	3	2	N/A
Cancer		2	N/A
Naïve		6	N/A
Total	18	36	N/A

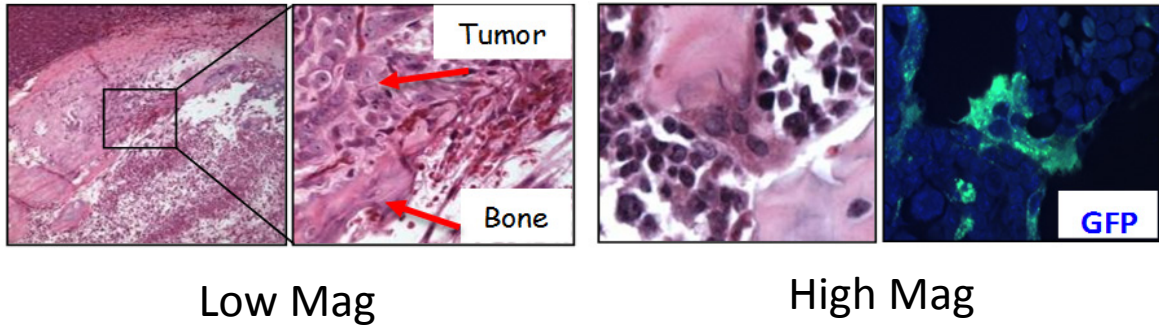
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Total # of Cores: 388

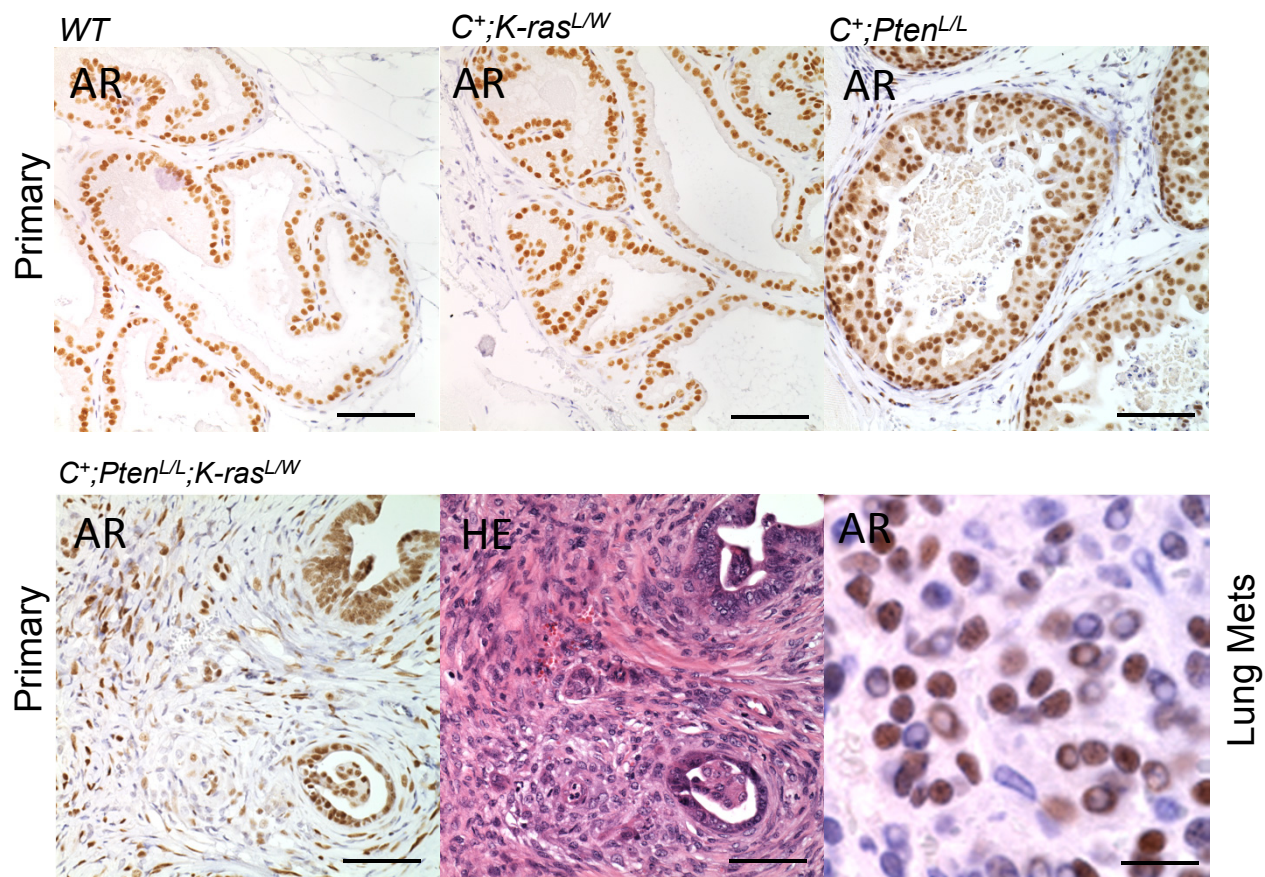
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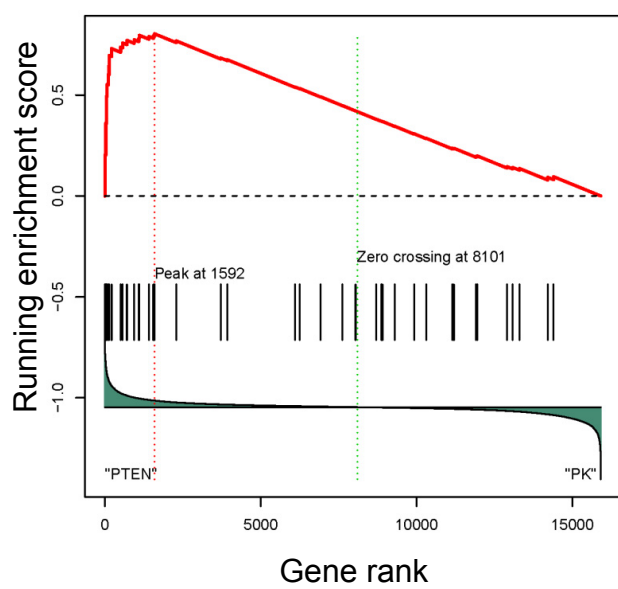
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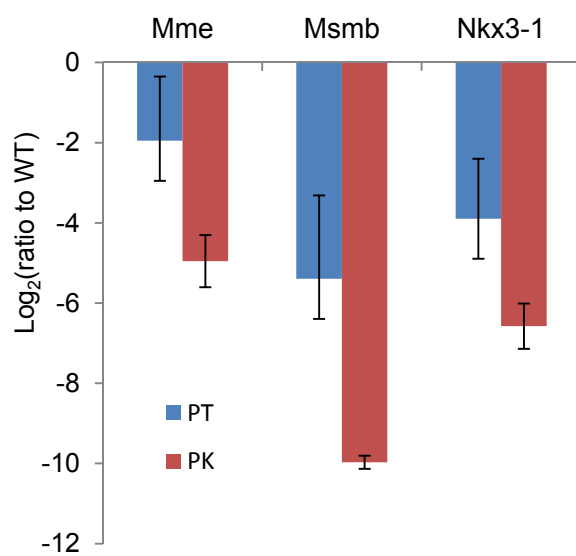
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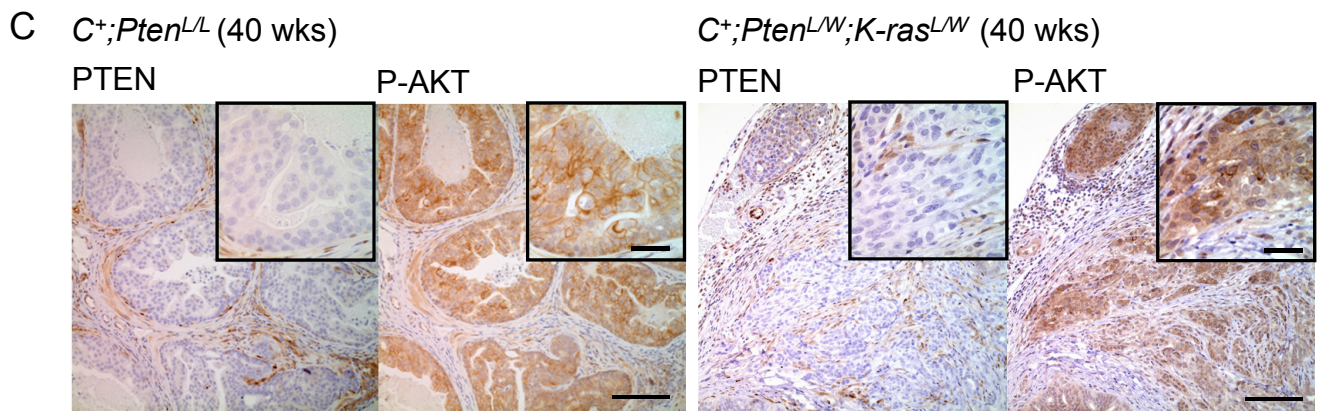
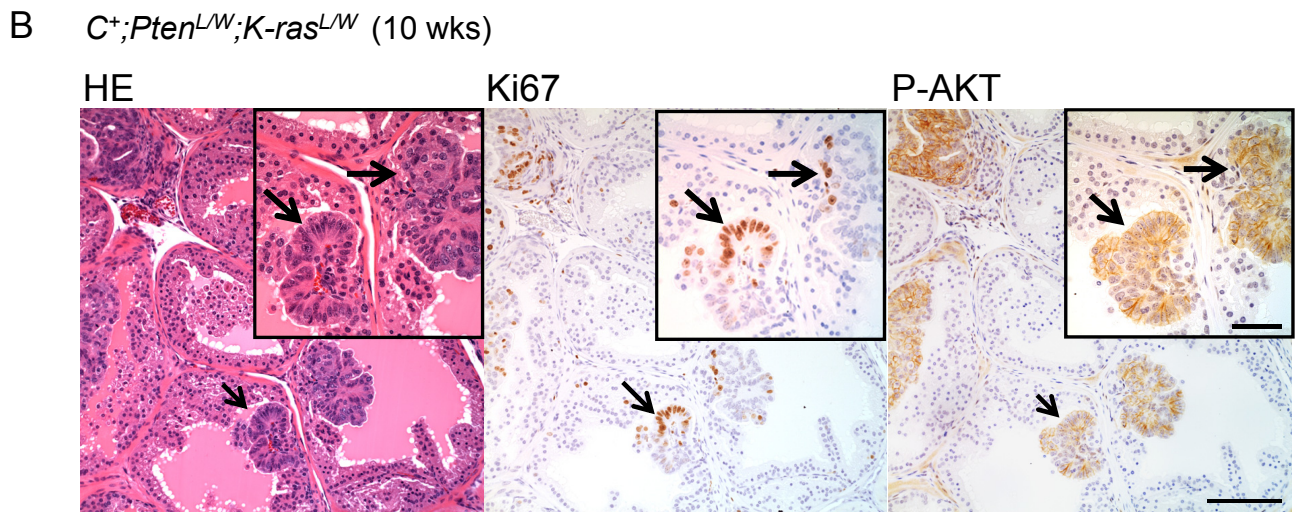
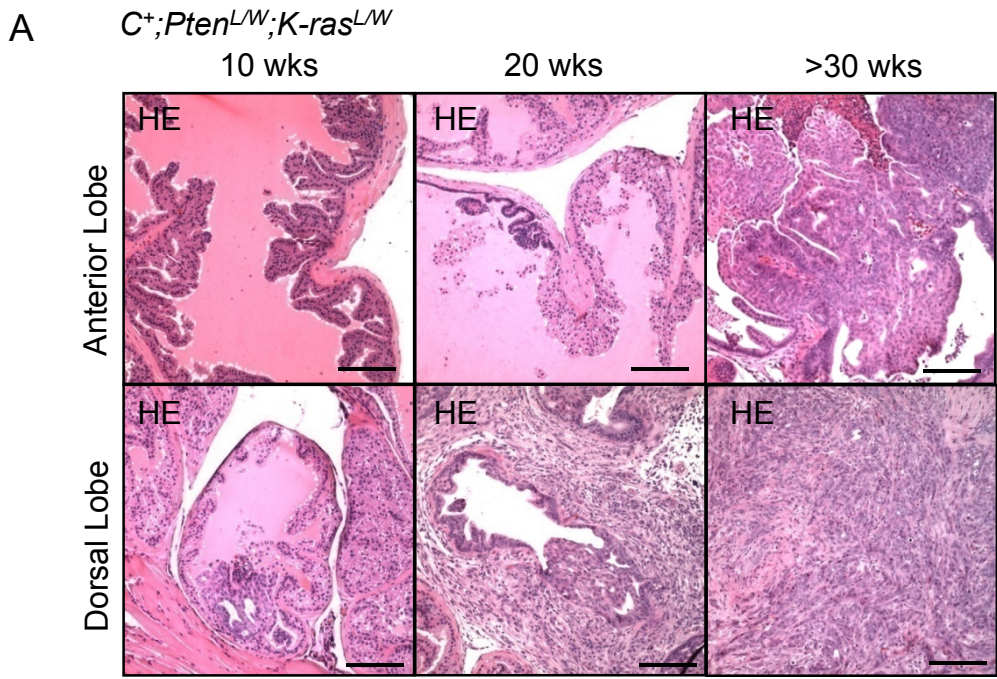


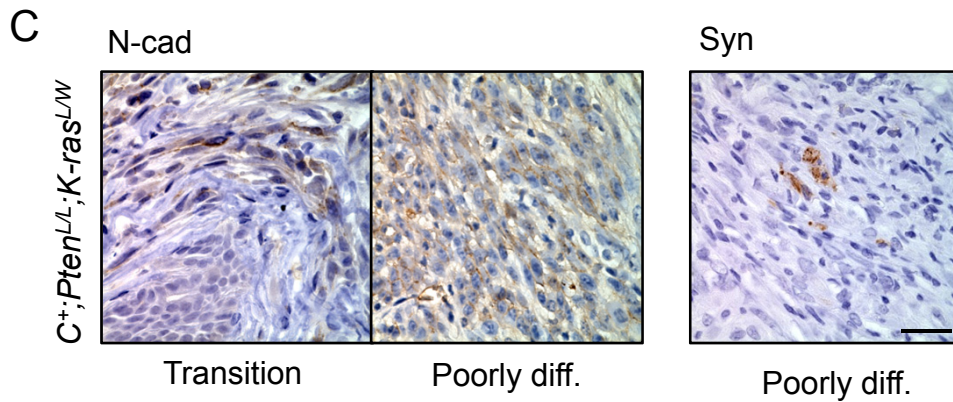
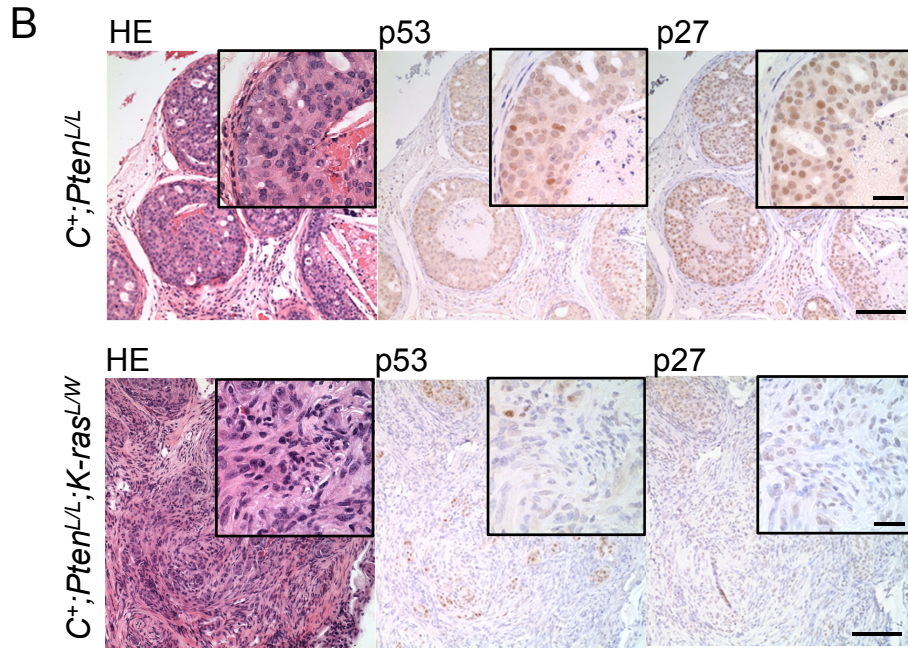
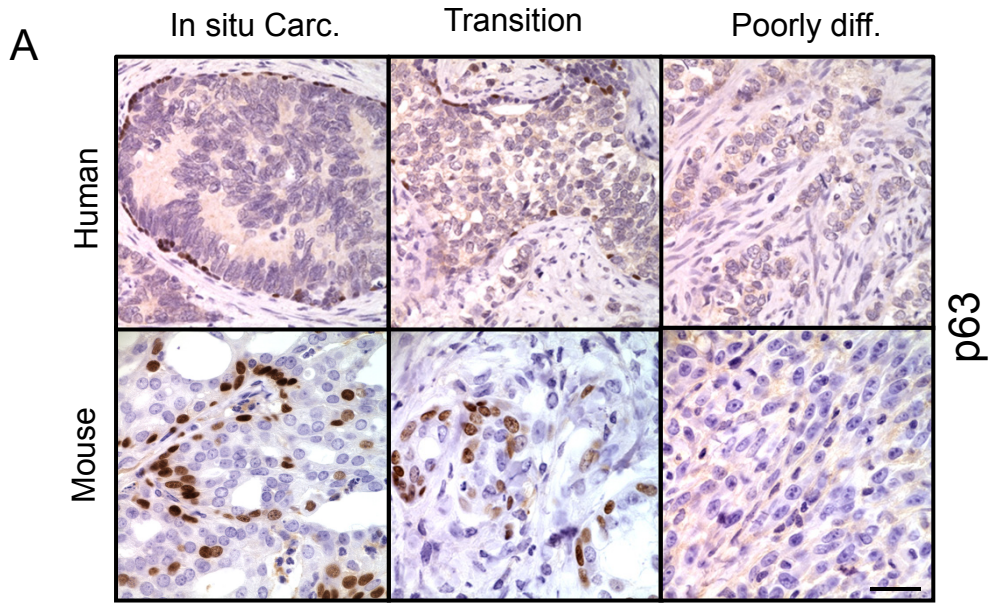
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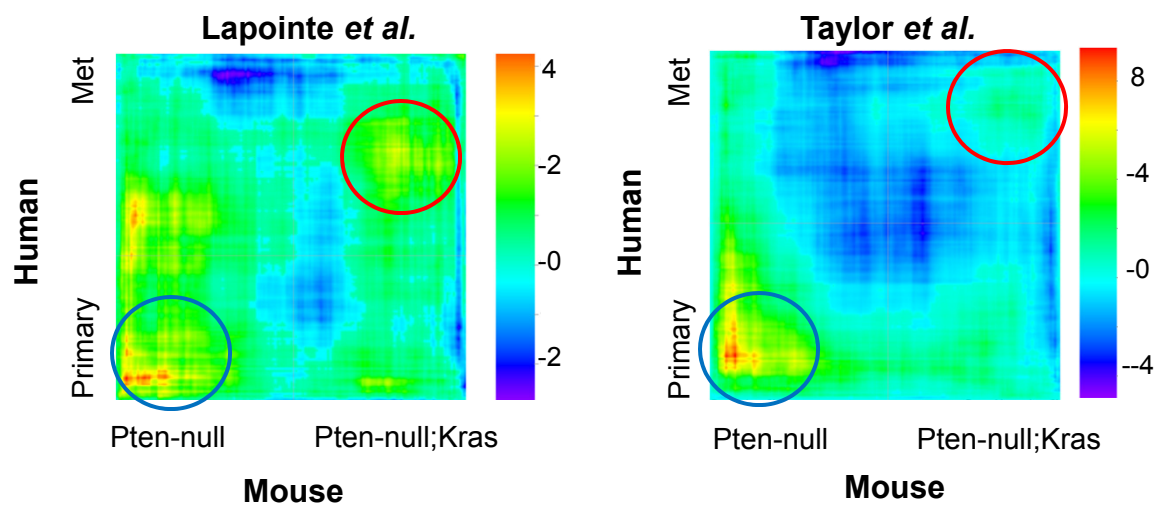
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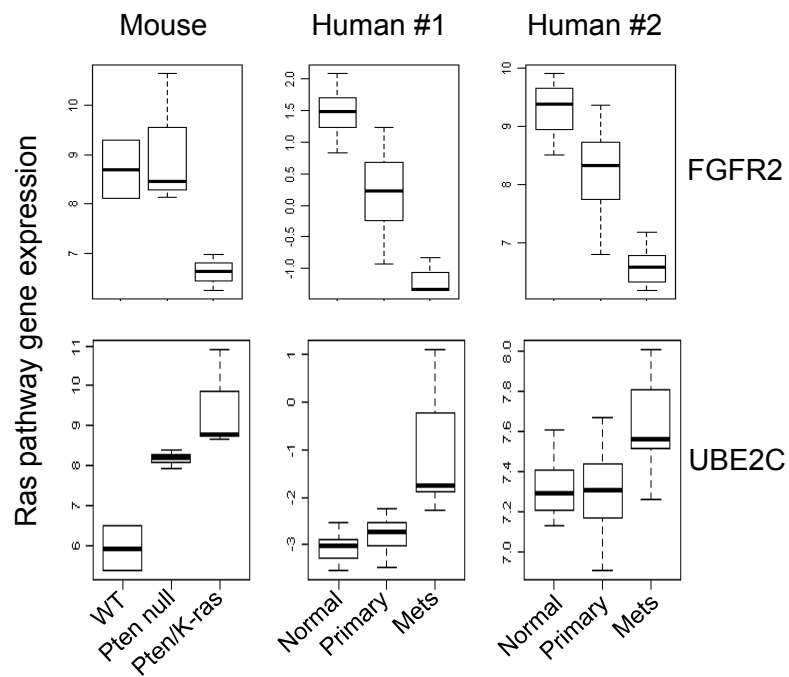




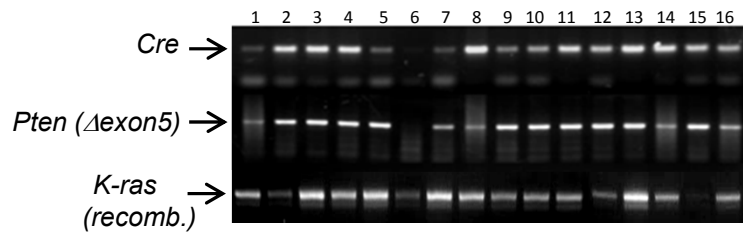
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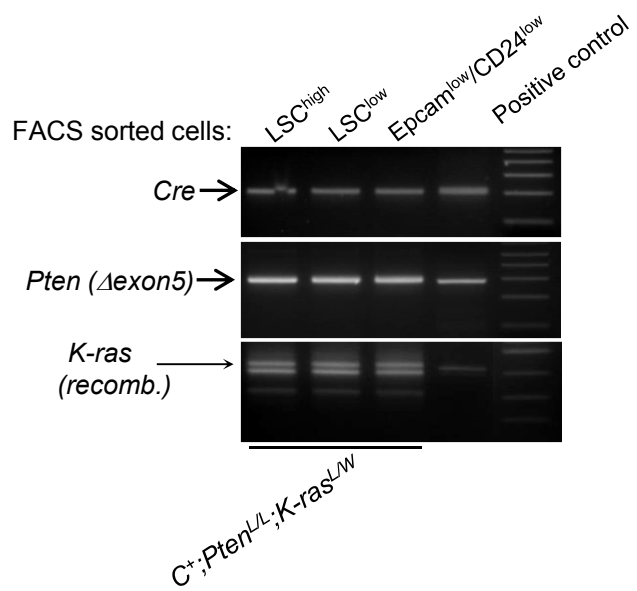
B



A



B



C

