Supplementary Information Table of Contents

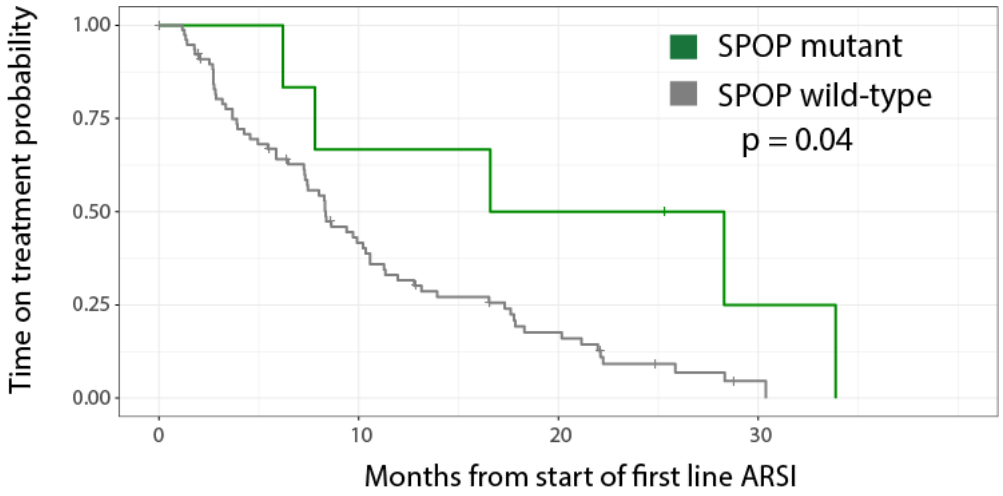


Figure S1: Kaplan-Meier analysis showing time on treatment with first-line ARSI for SPOP wild-type and SPOP-mutated tumors. P-value was generated from the logrank statistic.

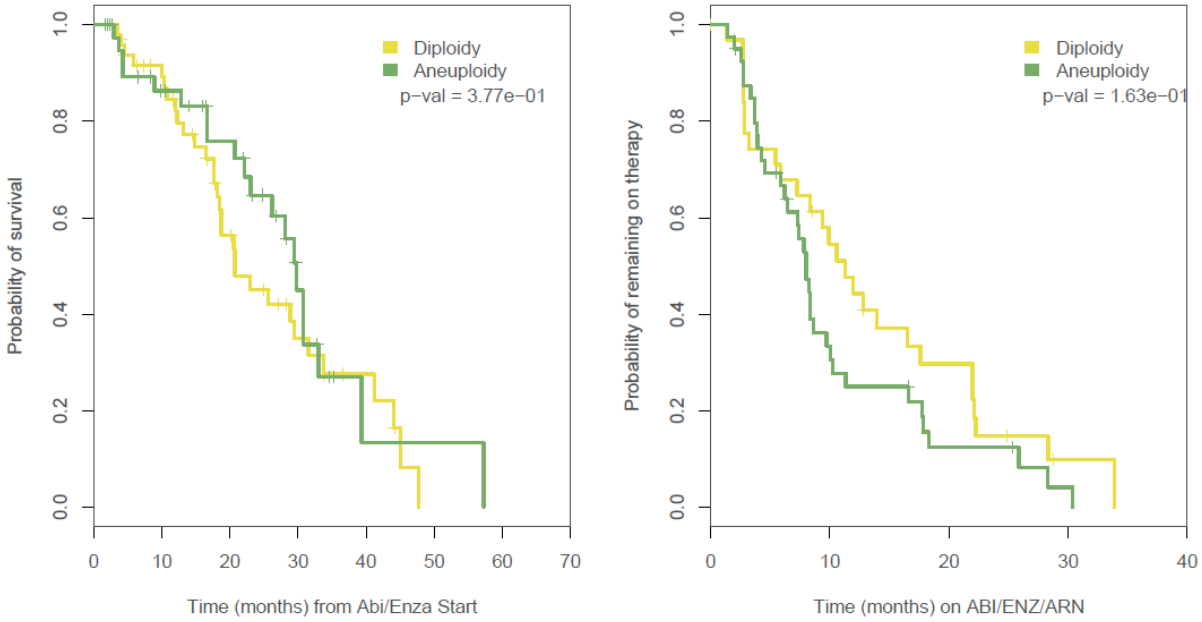
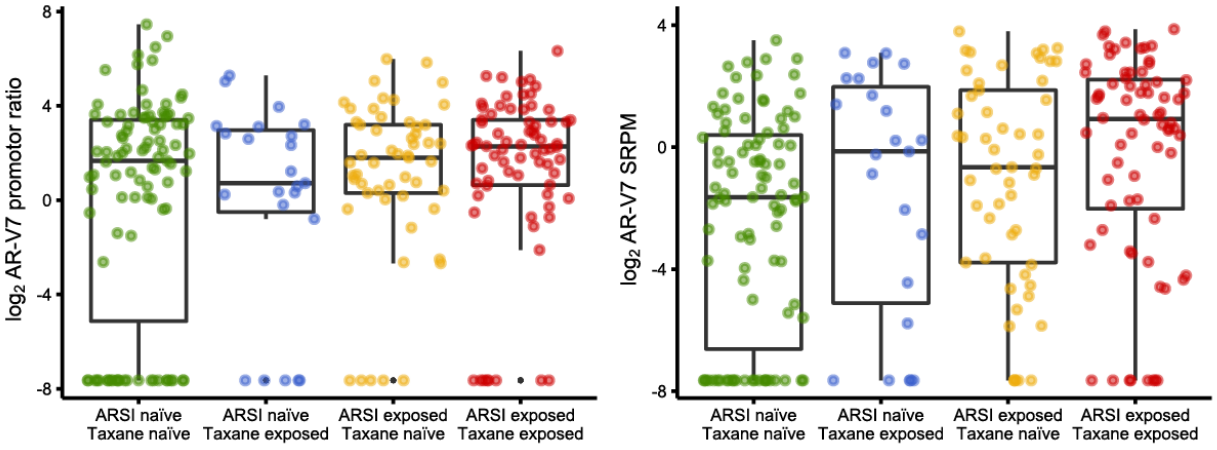


Figure S2: Kaplan-Meier analysis showing overall survival and time on treatment with first-line ARSI for diploid and aneuploid tumors. P-value was generated from the logrank statistic.



T-Test P-values

	ARSI naïve Taxane naïve	ARSI naïve Taxane exposed	ARSI exposed Taxane naïve
ARSI naïve Taxane exposed	0.997	NA	NA
ARSI exposed Taxane naïve	0.117	0.28	NA
ARSI exposed Taxane exposed	0.037	0.172	0.752

T-Test P-values

	ARSI naïve Taxane naïve	ARSI naïve Taxane exposed	ARSI exposed Taxane naïve
ARSI naïve Taxane exposed	0.254	NA	NA
ARSI exposed Taxane naïve	0.028	0.649	NA
ARSI exposed Taxane exposed	0	0.147	0.195

Figure S3: AR-V7 levels in relation to prior treatment exposure. AR-V7 level detected in PolyA libraries as ratio of AR-V7 reads / AR promoter 1-2 (Left) and as splice reads per million (SRPM) (Right) in relation to ARSI and taxane treatment exposure. AR-V7 expression is higher in tumors exposed to both an ARSI and a taxane relative to tumors that are naïve to both agents. P-values were generated using unpaired t-tests.

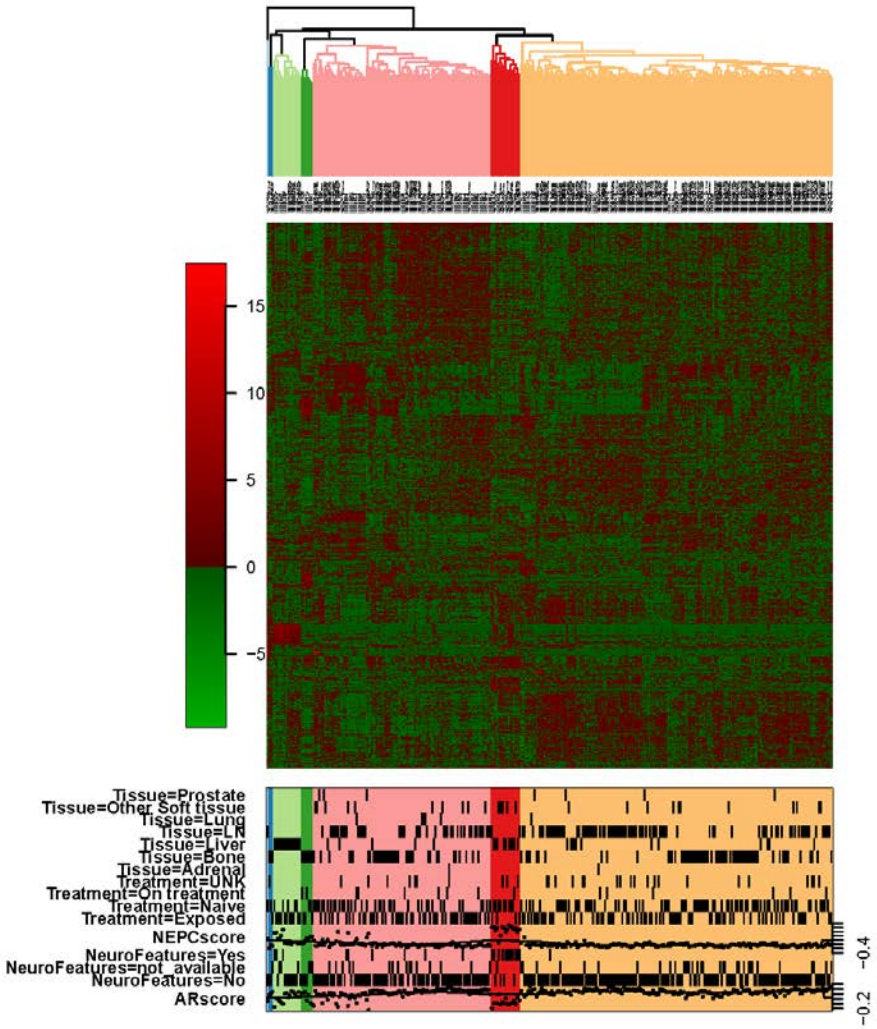


Figure S4: Unsupervised gene expression clustering analysis of study cohort using Pearson's correlation as metric. Analysis includes approximately 13,000 transcripts that passed a cross-cohort variance filter. The dendrogram identifies a cluster of tumors with high NEPC expression score. No clusters enriched for exposure to ARSIs were detected.

A

	Path_Adeno	Path_NE	Fisher Test	
nepc score < .4	240	7	OR	80.50
nepc score >= .4	6	15	p-value	5.82E-15
	other	P53.alt/RB1.alt		
nepc score < .4	282	18	OR	9.92
nepc score >= .4	14	9	p-value	1.91E-05
	other	P53.alt/RB1.alt		
Path_Adeno	230	16	OR	11.75
Path_NE	12	10	p-value	3.81E-06

B

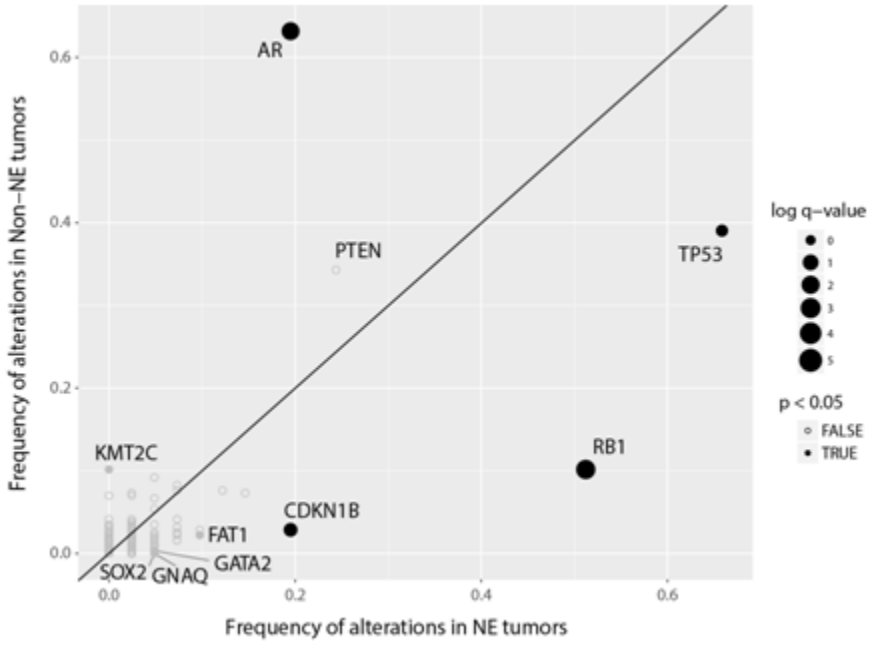


Figure S5: A. Associations between histopathology, NEPC expression score and TP53/RB1 genomic status. Top panel: Association between NEPC score low (<4) and high (>=4) tumors and histopathologic classification (Adenocarcinoma versus NE features). Middle panel: Association between NEPC score and genomic co-alteration in TP53 and RB1. Bottom panel: association between histopathologic classification and genomic co-alteration in TP53 and RB1. **B.** Enrichment of genomic alterations in histopathologic NE tumors versus non-NE (CRPC-adenocarcinoma) tumors.

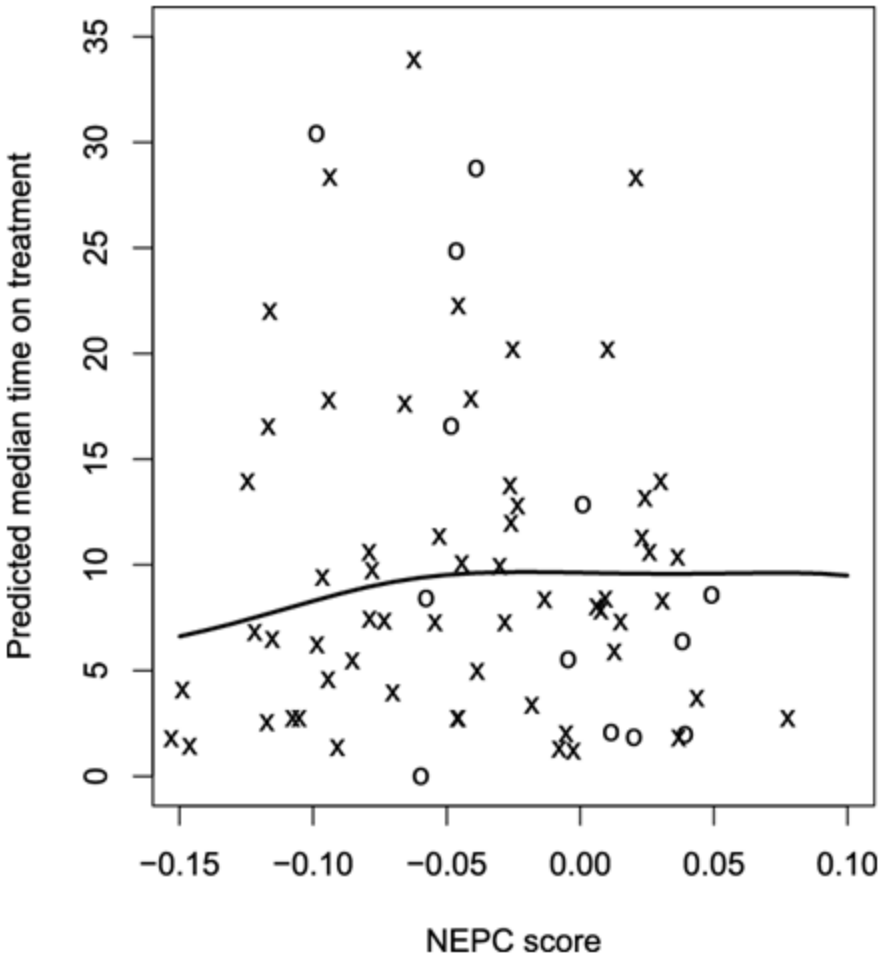


Figure S6: Association between NEPC score and time on treatment with a first-line ARSI for mCRPC. A p-value of 0.36 was derived from the distribution of the maximum logrank test statistic, for a NEPC score cutpoint of -0.02 that produced that maximum logrank statistic. X = off treatment event. O = censored event.

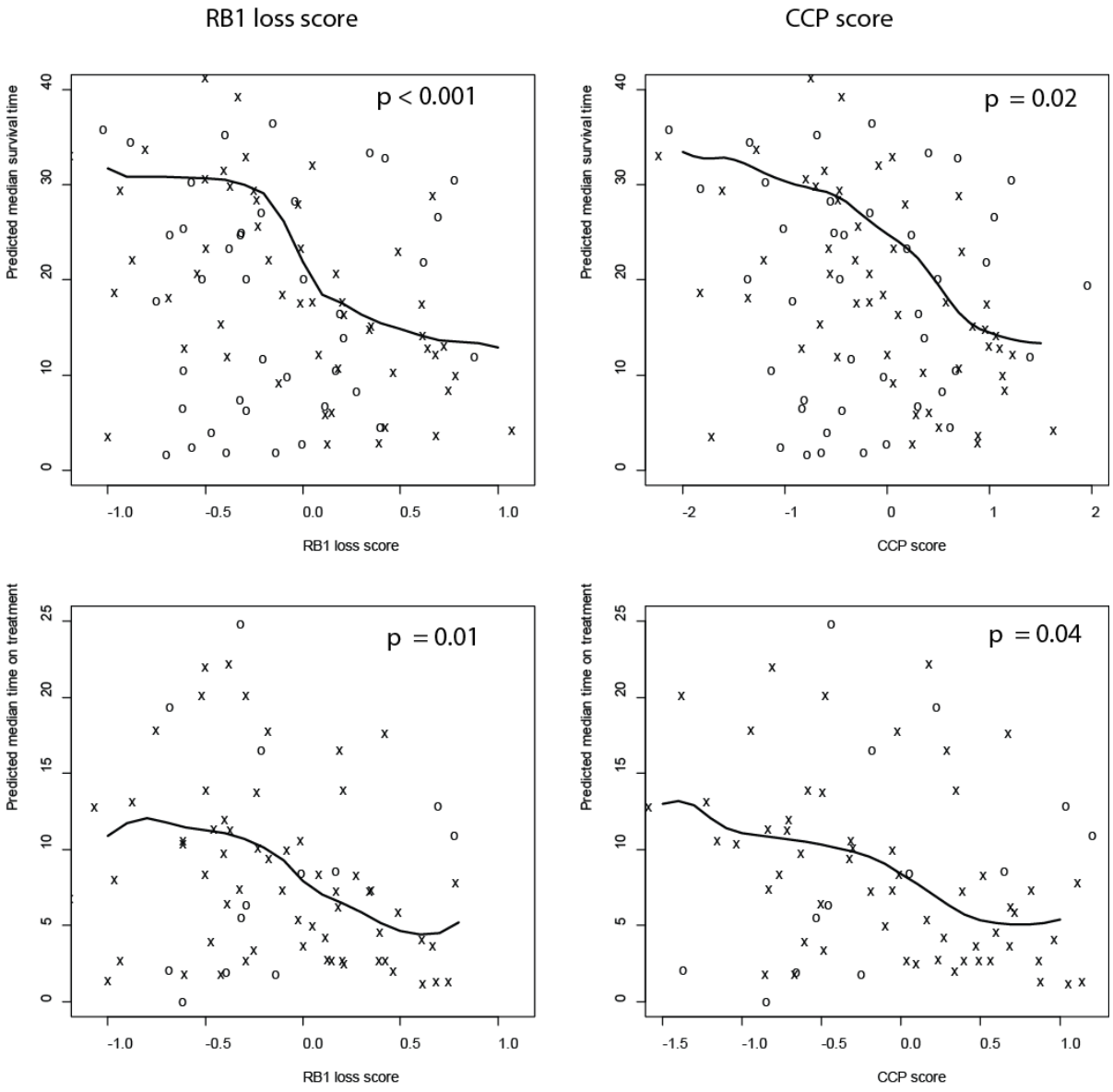


Figure S7: Association of RB1 loss score (left) and cell cycle progression (CCP) expression score (right) with overall survival from start of first-line ARSI (top) and time on treatment with first-line ARSI (bottom). P-values are derived from the logrank statistic. X = off treatment event. O = censored event.

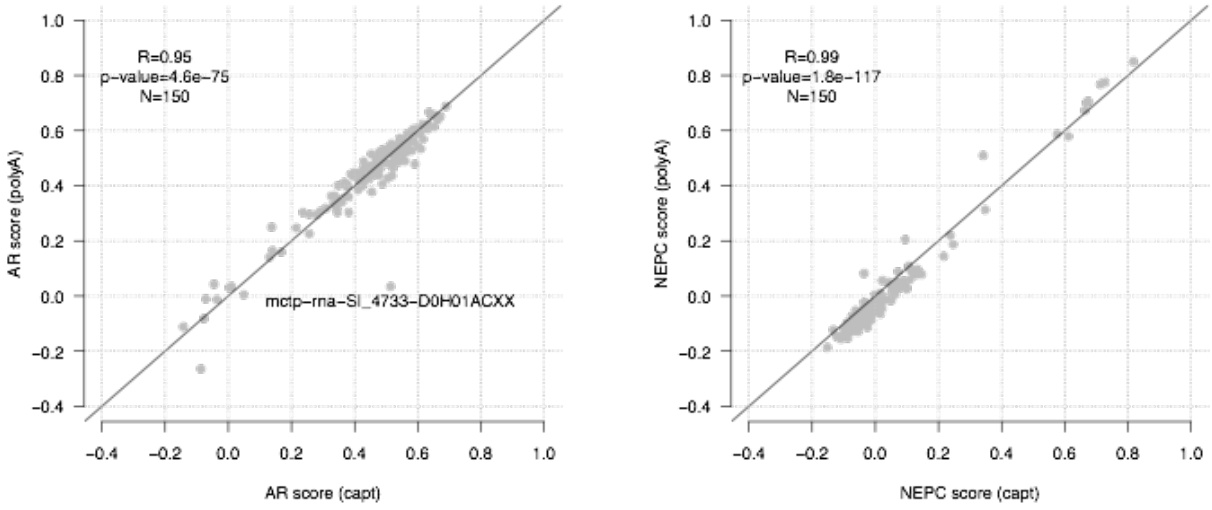


Figure S8: Correlation between expression scores derived from PolyA RNA sequencing libraries (Y-Axis) versus capture libraries (X-Axis) for AR output scores (left plot) and NEPC scores (right plot).

Clinical characteristic (N = 429 subjects)	**Value**
Median age at diagnosis (range) (Unknown for N = 50 patients)	61 (38-89)
Median age at biopsy (range) (Unknown for N = 15 patients)	67 (39-95)
Gleason score at diagnosis 6 7 8-10 Unknown	 N = 27 (6%) N = 103 (24%) N = 214 (50%) N = 85 (20%)
Median PSA at diagnosis (range) (Unknown for N = 81 patients)	14.0 (<0.05-16,275)
Median OS from biopsy	16.2 months

Table S1: Summary clinical characteristics for 429 patients with metastatic CRPC who underwent successful tumor profiling.

Gene_ID	Pathway	Alterations included
ATM	DNA repair	ATM:homdel mut
ATR	DNA repair	atr:homdel mut
BRCA1	DNA repair	brca1:homdel mut
BRCA2	DNA repair	brca2:homdel mut
CDK12	DNA repair	cdk12:homdel mut
FANCA	DNA repair	fanca:homdel mut
MRE11A	DNA repair	mre11:mut
PALB2	DNA repair	palb2:mut
CCND1	CELL CYCLE	ccnd1:mut amp
CDK4	CELL CYCLE	cdk4:mut amp
CDKN1B	CELL CYCLE	cdkn1b:mut homdel
RB1	CELL CYCLE	rb1:mut homdel
CDKN2A	CELL CYCLE	cdkn2a:mut homdel
ARID1A	Epigenetic	ARID1A:mut
ARID2	Epigenetic	ARID2:mut
ARID4A	Epigenetic	ARID4A:mut
KDM6A	Epigenetic	KDM6A:mut
KMT2A	Epigenetic	KMT2A:mut
KMT2C	Epigenetic	KMT2C:mut
KMT2D	Epigenetic	KMT2D:mut
MBD1	Epigenetic	MBD1:mut
SETD2	Epigenetic	SETD2:mut
SETDB1	Epigenetic	SETDB1:mut
SMARCA1	Epigenetic	SMARCA1:mut
SMARCAD1	Epigenetic	SMARCAD1:mut
AKT1	PI3K	AKT1:AMP MUT
MTOR	PI3K	MTOR:MUT
PIK3CA	PI3K	PIK3CA:AMP MUT

PIK3CB	PI3K	PIK3CB:AMP MUT
PIK3R1	PI3K	PIK3R1:HOMDEL MUT
PIK3R2	PI3K	PIK3R2:AMP MUT
PIK3R3	PI3K	PIK3R3:HOMDEL MUT
PTEN	PI3K	PTEN:HOMDEL MUT
TSC1	PI3K	TSC1:HOMDEL MUT
TSC2	PI3K	TSC2:HOMDEL MUT
BRAF	RAS/MAPK	braf:mut amp
HRAS	RAS/MAPK	hras:mut amp
KRAS	RAS/MAPK	kras:mut amp
MAP2K1	RAS/MAPK	map2k1:mut
MAP3K1	RAS/MAPK	map3k1:mut
NF1	RAS/MAPK	nf1:mut homdel
RASA1	RAS/MAPK	rasa1:mut homdel
APC	WNT	apc:mut homdel
AXIN1	WNT	axin1:mut homdel
AXIN2	WNT	axin2:mut homdel
CTNNB1	WNT	ctnnb1:mut
RNF43	WNT	rnf43:mut homdel
ZNRF3	WNT	znrf3:mut homdel

Table S2: Pathway classifications of genes altered in mCRPC. Indicated are gene names, pathway in which the gene/protein is functional based on current knowledge, and gene alterations that are considered potentially biologically-relevant for that gene.

Gene_ID	Type of manual copy number assessment
APC	HOMDEL
AR	AMP
ATM	HOMDEL
BRCA1	HOMDEL
BRCA2	HOMDEL
CDK12	HOMDEL
CDKN1B	HOMDEL
CDKN2A	HOMDEL
CHD1	HOMDEL
FANCA	HOMDEL
MLH1	HOMDEL
MSH2	HOMDEL
NKX3-1	HOMDEL
PIK3CB	AMP
PIK3R1	HOMDEL
PTEN	HOMDEL
RB1	HOMDEL
TP53	HOMDEL
ZBTB16	HOMDEL
ZFHX3	HOMDEL

Table S3: Genes that underwent secondary manual copy number assessment. AMP = amplification. HOMDEL = homozygous deletion