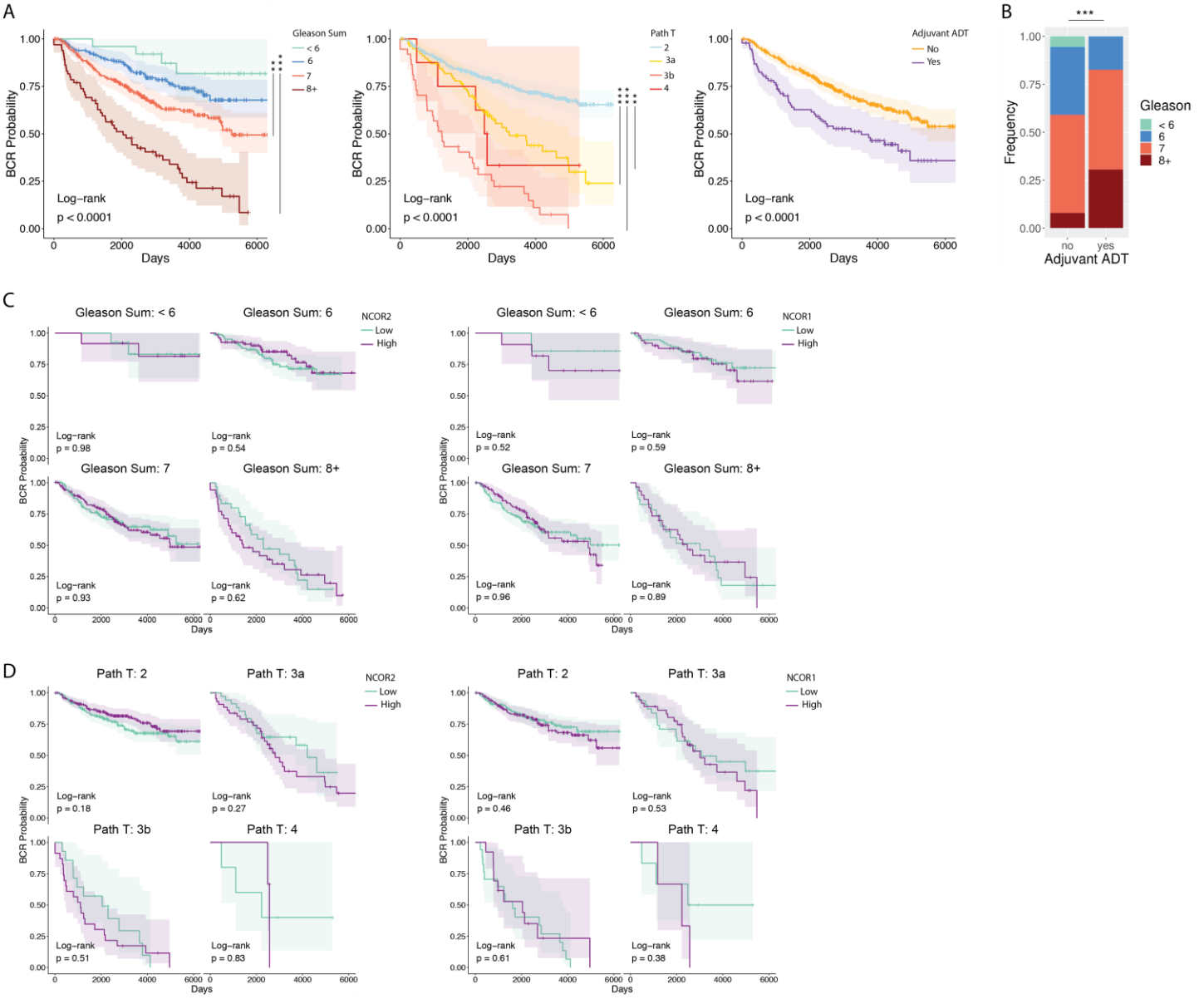


Figure S1: **Relationships between clinical characteristics and NCOR2 expression in PC patient-tissue microarray radical proctectomy samples. Related to Figure 1D,E.** A) Associations of Gleason sum (left), pathologic stage (middle) and adjuvant ADT (right) with BCR survival. Overall log-rank test is shown, and significance of individual comparisons from univariate regression analysis are noted. B) Distribution of Gleason scores between patients that did or did not receive adjuvant ADT. Significance was determined by chi-square test. C) BCR survival assessment of patients with high and low expression of NCOR2 (left) and NCOR2 (right). NCOR associated survival was compared within sub-cohorts of patients stratified by Gleason sum and D) pathologic stage.

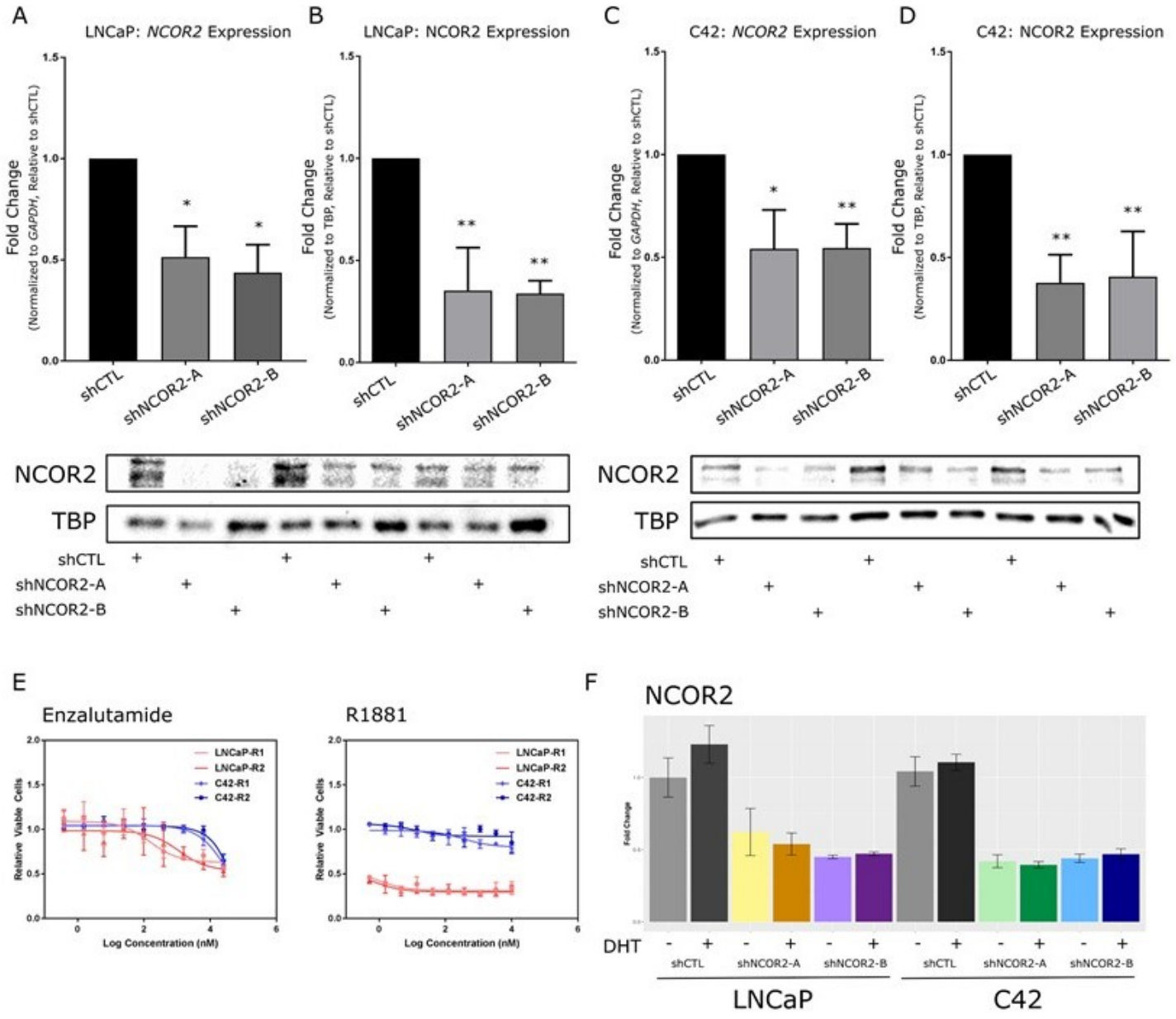


Figure S2: Characterization of sh-mediated NCOR2 knockdown PC cell lines. Related to Figures 4, 5. A) NCOR2 gene expression in LNCaP-shCTL and LNCaP-shNCOR2 cells. B) NCOR2 protein expression (below) and quantification (above) in LNCaP-shCTL and LNCaP-shNCOR2 cells. C) NCOR2 gene expression in C4-2-shCTL and C4-2-shNCOR2 cells. D) NCOR2 protein expression (below) and quantification (above) in C4-2-shCTL and C4-2-shNCOR2 cells. E) Dose response of LNCaP (blue) and C4-2 (red) to enzalutamide (left) and R1881 (right). F) NCOR2 gene expression in shCTL and shNCOR2 cell lines exposed to DHT. All quantified data in this figure reported as mean +/- SD.

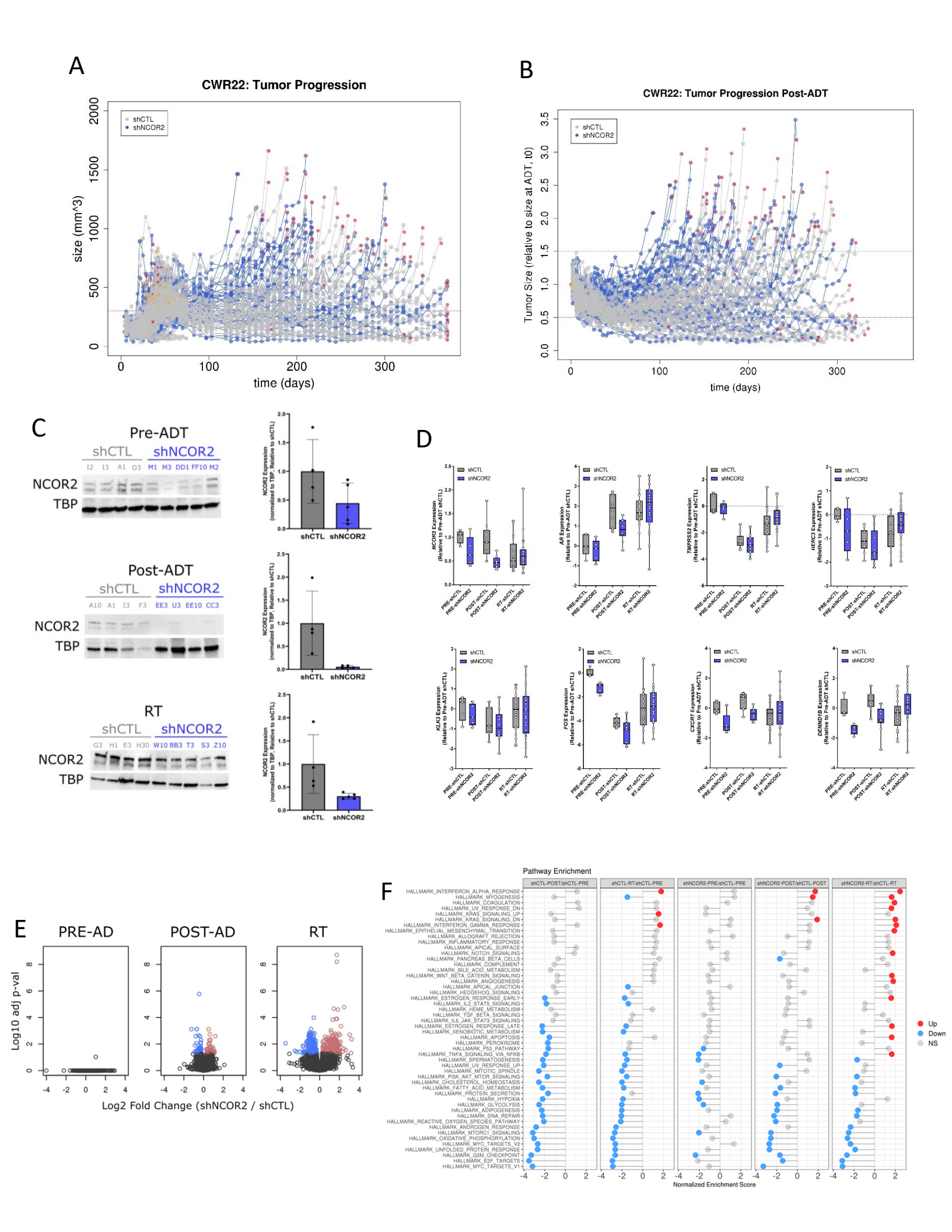

A
CWR22: Tumor Progression
shCTL
shNCOR2
size (mm^3)
time (days)
B
CWR22: Tumor Progression Post-ADT
Tumor Size (relative to size at ADT, t0)
C
Pre-ADT
Post-ADT
RT
NCOR2
TBP
NCOR2 Expression (normalized to TBP, Relative to shCTL)
D
E
PRE-AD
POST-AD
RT
Log10 adj p-val
Log2 Fold Change (shNCOR2 / shCTL)
F
Pathway Enrichment
shCTL-POST/shCTL-PRE
shCTL-RT/shCTL-PRE
shNCOR2-PRE/shCTL-PRE
shNCOR2-POST/shCTL-POST
shNCOR2-RT/shCTL-RT
Up
Down
NS
Normalized Enrichment Score

Figure S3: Stable reduction of NCOR2 expression in CWR22 xenograft model associate with lineage-related gene expression changes. Related to Figure 2. A) Absolute tumor growth and B) androgen withdrawal normalized growth of all tumors in the study. C) Immunoblots of NCOR2 protein expression and quantification in CWR22 shCTL and shNCOR2 tumors at Pre-ADT, Post-ADT, and Recurrency (RT). Data represented as mean with SD. D) RT-qPCR of select androgen regulated genes at different stages of disease progression in shCTL and shNCOR2 tumors. Data summarized as boxplots representing lower, middle, and upper quartiles. Whiskers indicate maximum and minimum values, excluding outliers defined as 1.5*IQR. E) Volcano plots depicting NCOR2-dependent DEGs (red = upregulated, blue = downregulated) determined at different stages of disease. F) GSEA summary of the top enriched Hallmark gene sets associated with DEGs identified in post-AD and RT relative to pre-AD tumors, and NCOR2-dependent DEGs at each stage of disease.

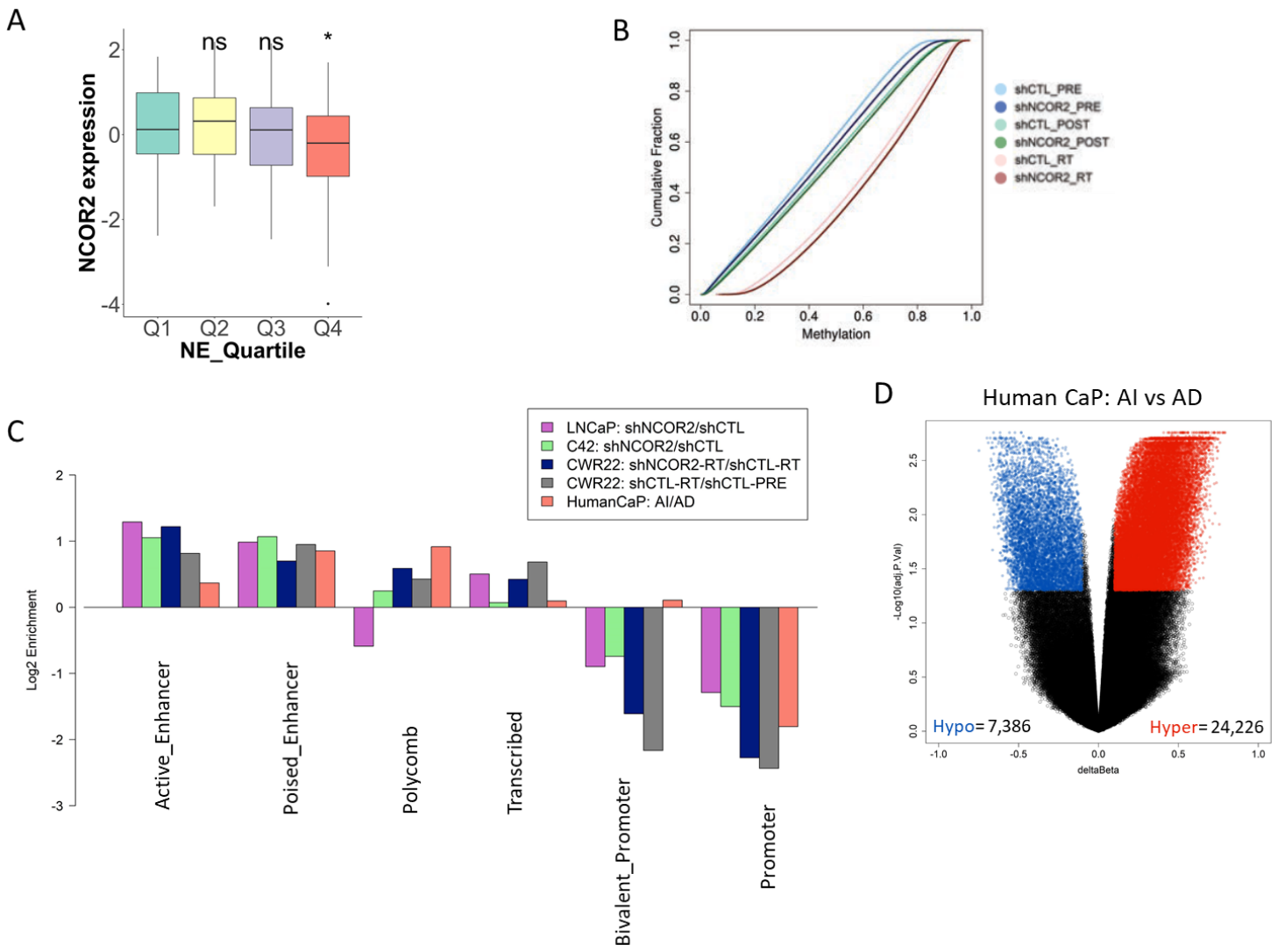


Figure S4: Reduced NCOR2 expression associate with neuroendocrine-like prostate cancer patient cohorts and DNA hypermethylation at enhancer regions *in vivo*. Related to Figure 3. A) NCOR2 expression of patients from the SU2C post ADT cohort divided by quartiles of neuroendocrine scores (NE.quartiles) for each tumor. Data summarized as boxplots representing lower, middle, and upper quartiles. Whiskers indicate maximum and minimum values. B) Cumulative distribution plots showing the total methylation levels observed within each CWR22 group. C) Relative enrichment of DMPs within chromHMM categories for respective comparisons. D) Volcano plots representing methylation changes identified in human PC samples (androgen independent (AI) relative to androgen dependent (AD)). Determined DMPs are shown in blue (hypomethylated) and red (hypermethylated).

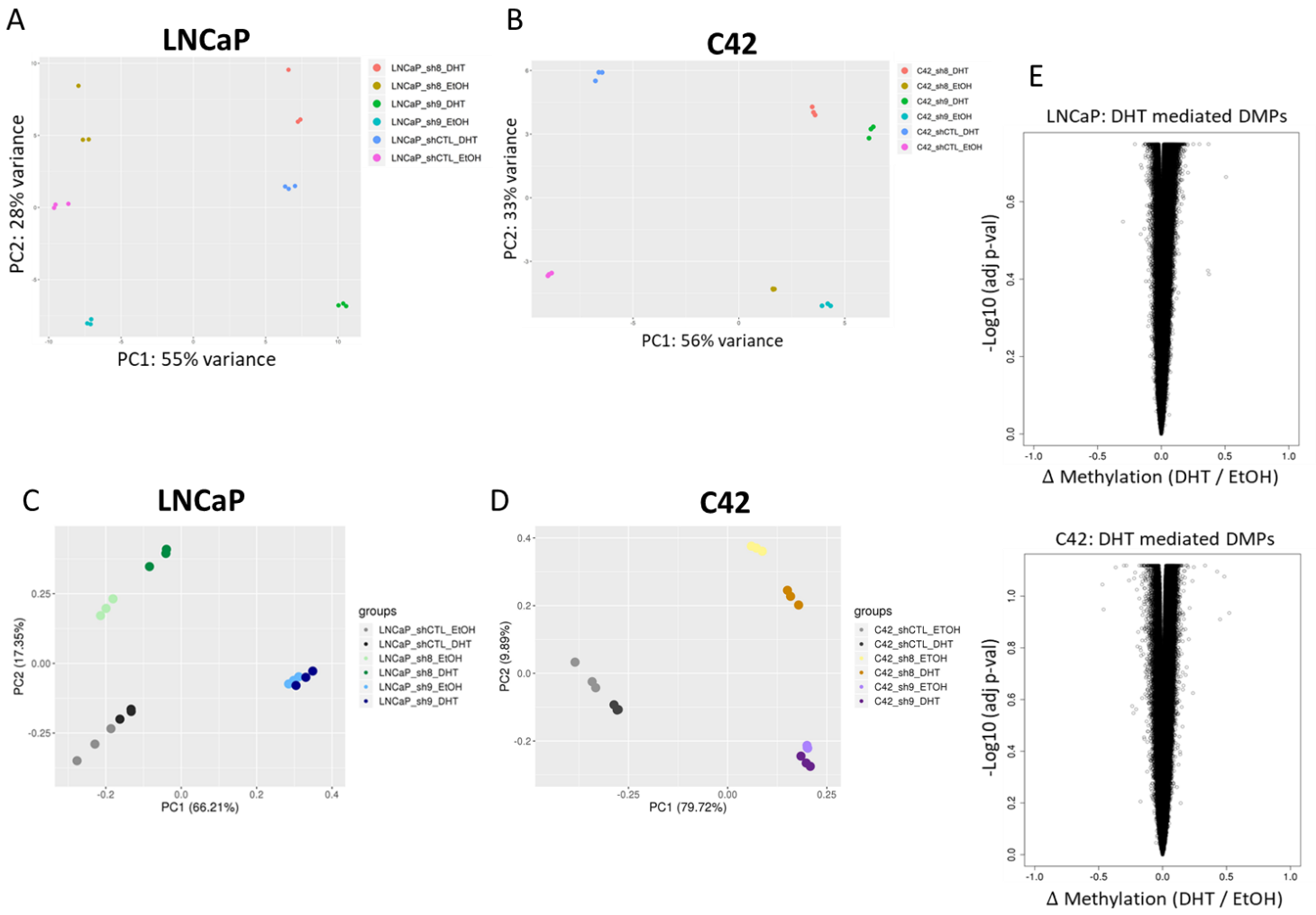


Figure S5: Principal component analyses of LNCaP and C4-2 samples based on gene expression and DNA methylation changes. Related to Figures 4 and 5. A) Principal component analyses for LNCaP (left) and C4-2 (right) samples based on total gene expression profiles. B) Principal component analyses for LNCaP (left) and C4-2 (right) samples based on total DNA methylation profiles. C) Volcano plots representing methylation changes identified upon DHT exposure in LNCaP (top) and C4-2 (bottom) cells. Determined DMPs are shown in blue (hypomethylated) and red (hypermethylated).

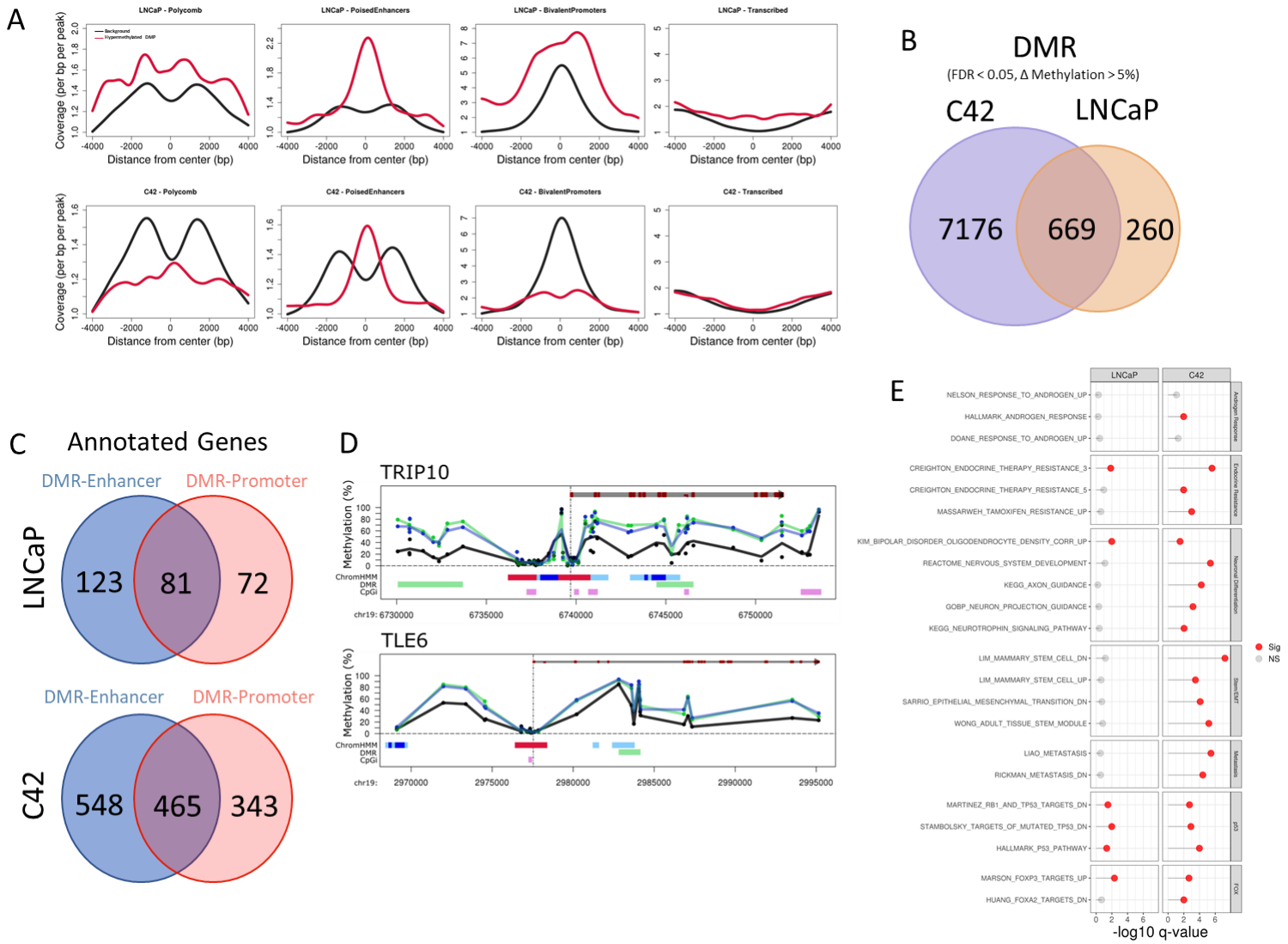
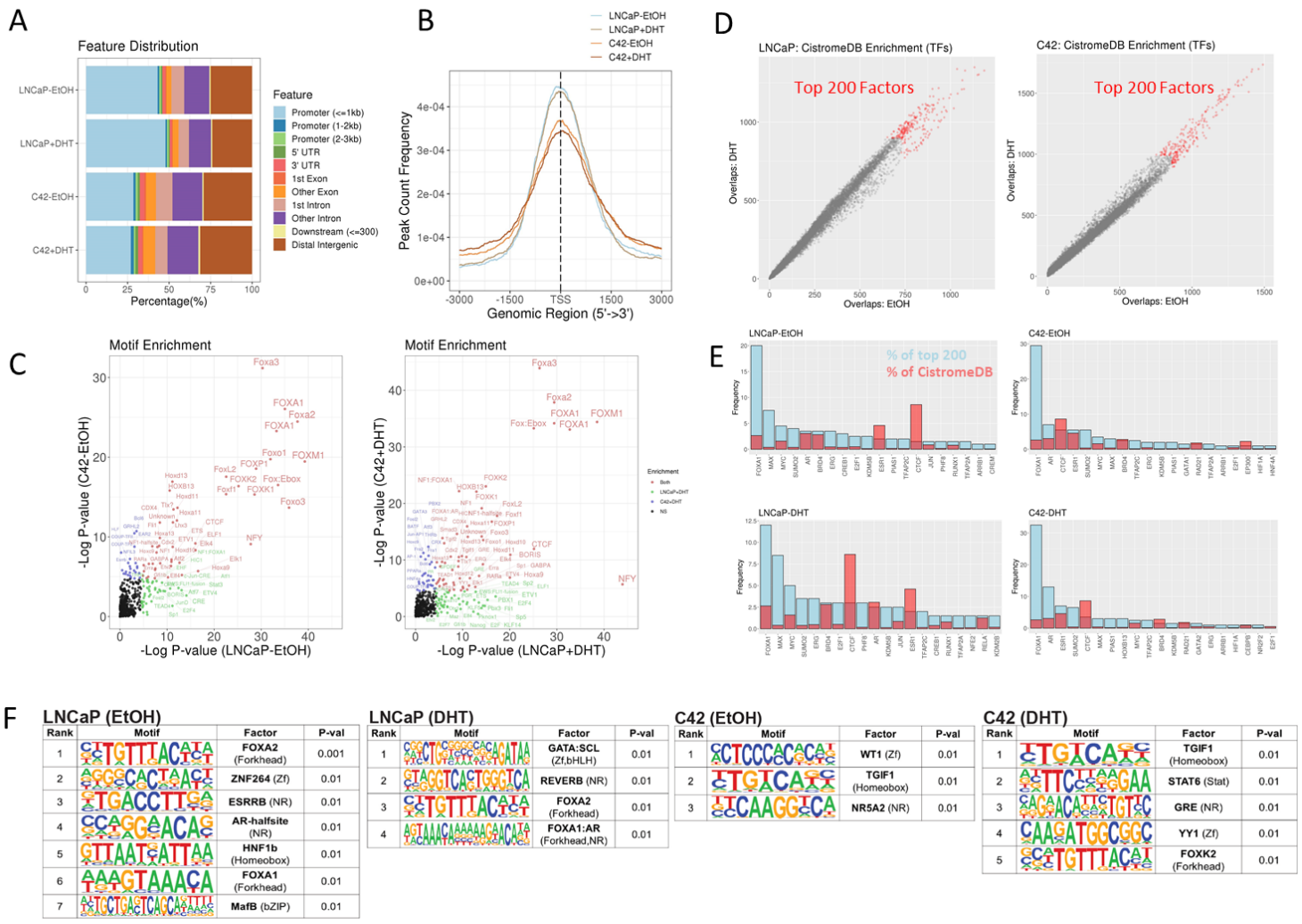


Figure S6: Functional analyses of DNA methylation changes in LNCaP and C42 cells in basal or +DHT conditions. Related to Figure 5. A) Peak centered densities of non-DMP CpG sites (black) or hypermethylated DMPs (red) centered at chromHMM regions. B) Venn diagram of DMRs identified in each cell. C) Venn diagram of annotated DMR-enhancer and DMR-promoter genes identified in LNCaP (top) and C4-2 (bottom). D) Representative genomic view of an NCOR2 dependent gene locus with annotated enhancer hypermethylation (TRIP10, TLE6). E) Selected significant enriched pathways from GSEA analysis of DMR-enhancer associated genes in both LNCaP (left column) and C4-2 (right column) related to lineage plasticity and hormone therapy resistance.



F

LNCaP (EtOH)

Rank	Motif	Factor	P-val
1		**FOXA2** (Forkhead)	0.001
2		**ZNF264** (Zf)	0.01
3		**ESRRB** (NR)	0.01
4		**AR-halfsite** (NR)	0.01
5		**HNF1b** (Homeobox)	0.01
6		**FOXA1** (Forkhead)	0.01
7		**MafB** (bZIP)	0.01

LNCaP (DHT)

Rank	Motif	Factor	P-val
1		**GATA:SCL** (Zf,bHLH)	0.01
2		**REVERB** (NR)	0.01
3		**FOXA2** (Forkhead)	0.01
4		**FOXA1:AR** (Forkhead,NR)	0.01

C42 (EtOH)

Rank	Motif	Factor	P-val
1		**WT1** (Zf)	0.01
2		**TGIF1** (Homeobox)	0.01
3		**NR5A2** (NR)	0.01

C42 (DHT)

Rank	Motif	Factor	P-val
1		**TGIF1** (Homeobox)	0.01
2		**STAT6** (Stat)	0.01
3		**GRE** (NR)	0.01
4		**YY1** (Zf)	0.01
5		**FOXK2** (Forkhead)	0.01

Figure S7: Functional analyses of the NCOR2 cistromes in LNCaP and C42 in basal or +DHT conditions. Related to Figures 6 and 7. A) Proportional annotations of determined NCOR2 cistromes to gene regions. B) Density plot of NCOR2 binding around TSS loci. C) Motif enrichments, comparing cistromes in untreated (left) and DHT treated (right) cells between cell lines. D) Scatterplot representing total overlaps identified between LNCaP (left) and C4-2 (right) cistromes and all transcription factor datasets available in the CistromeDB. The top 200 enriched datasets are shown in red. E) The top 20 most frequently observed factors within the top 200 enriched datasets for each NCOR2 cistrome. The observed frequencies (blue) were compared to the background frequencies (red), and factors occurring at rates similar to background (< 1.2x enrichment) were removed from subsequent analyses. F) Known motif enrichments of regions found in both the NCOR2-cistome and identified super-enhancers in LNCaP and C42 cells, in DHT-supplemented (DHT) and untreated (EtOH) conditions. All significantly enriched motifs (p-val < 0.01) are shown for each condition.

	Total					
NCOR2	564					
Hscore	Min	Q25	Median	Q75	Max	
NCOR2	0	55.06	91.5	127.57	246	
BMI	Min	Q25	Median	Q75	Max	NA
NCOR2	18.46	25.63	28.05	30.86	51.42	10
Pre-RP PSA	Min	Q25	Median	Q75	Max	NA
NCOR2	0	4.25	5.6	8	41.9	38
Age at surgery	Min	Q25	Median	Q75	Max	
NCOR2	39.18	55.04	60.08	65.74	74.62	
Gleason Sum	< 6	6	7	8+		
NCOR2	26	183	290	65		
PathT	2X	3a	3b	4		
NCOR2	437	81	38	8		
Adjuvant ADT	No	Yes				
NCOR2	472	92				
Race	White	Black	Other	NA		
NCOR2	520	34	6	4		

Table S1: **Clinical characteristics of Prostate Cancer patient tissue microarray of radical proctectomy (RP) samples. Related to Figure 1D.** Samples were evaluated for NCOR2 expression IHC (Hscore), and other clinical parameters such as body mass index (BMI), PSA level prior to RP (Pre-RP PSA), age at surgery, Gleason score sum, pathological scoring (PathT), if adjuvant ADT was received, and race.

NCOR2: H-score Linear Regression Analysis

	Dependent variable: Hscore							
	Hscore							
	Race: White	BMI: Normal (<	PSA: < 2.5	Gleason: < 6	Adjuvant ADT:	Age: < 55	Path Stage: 2	Multivariate
Race: Black	-16.750							-17.854
	-8.752							-9.319
Race: Other	-2.485							-2.206
	-20.302							-20.13
BMI: Overweight (> 25; < 30)		-17.147						-18.168
		-5.683						-5.759
BMI: Obese (> 30)		-8.942						-11.351
		-6.103						-6.267
PSA: > 2.5; < 4			-6.068					4.01
			-9.416					-9.8
PSA: > 4; < 10			-16.000					-3.384
			-6.938					-7.638
PSA: > 10			-22.786					-14.662
			-8.675					-9.184
Gleason: 6				-14.707				-22.052
				-10.376				-10.44
Gleason: 7				-7.589				-14.234
				-10.135				-10.222
Gleason: 8+				-4.755				-23.934
				-11.488				-12.08
Adjuvant ADT: TRUE					26.655			25.459
					-5.539			-6.511
Age: 55-65						-6.573		-7.361
						-5.208		-5.362
Age: 65+						-3.909		-6.004
						-5.707		-5.949
Path Stage: 3b							5.502	7.796
							-5.981	-6.331
Path Stage: 3a							17.113	11.617
							-8.363	-8.994
Path Stage: 4							-13.101	-8.877
							-17.641	-17.655
Constant	94.810	105.006	108.433	102.896	89.326	97.848	91.916	127.774
	-2.168	-4.847	-6.411	-9.709	-2.237	-4.204	-2.365	-12.792
Observations	560	554	526	564	564	564	564	517
R^2	0.007	0.017	0.017	0.007	0.04	0.003	0.01	0.095
Adjusted R^2	0.003	0.014	0.011	0.002	0.038	-0.001	0.004	0.066
Residual Std. Error	49.444 (df =	49.194 (df =	49.246 (df =	49.507 (df =	48.604 (df = 562)	49.568 (df =	49.445 (df =	47.975 (df = 500)
F Statistic	1.834 (df = 2;	4.862 (df = 2;	2.972 (df = 3;	1.331 (df = 3;	23.157 (df = 1;	0.800 (df = 2;	1.801 (df = 3;	3.265 (df = 16;
Note:								*p<0.1;**p<0.05;***p<0.01

Table S2: Univariate regression analyses evaluating associations between NCOR2 expression and PC clinical characteristics. Related to Figure 1E.

BCR Cox Regression Analysis

	Dependent variable: time to BCR							
	Race:	BMI: Normal (<	PSA: < 2.5	Gleason: < 6	Adjuvant ADT:	Age: < 55	Path Stage: 2	Multivariate
Race: Black	0.24							0.152
	-0.327							-0.354
Race: Other	0.537							-0.48
	-0.713							-0.751
BMI: Overweight (> 25;		0.219						0.336
		-0.344						-0.378
BMI: Obese (> 30)		0.122						0.274
		-0.255						-0.296
PSA: > 2.5; < 4		0.411						0.383
		-0.295						-0.333
PSA: > 4; < 10			0.037					0.026
			-0.204					-0.213
PSA: > 10			0.012					0.098
			-0.223					-0.237
Gleason: 6				0.731				0.712
				-0.527				-0.532
Gleason: 7				1.255				0.998
				-0.513				-0.52
Gleason: 8+				2.218				1.482
				-0.523				-0.546
Adjuvant ADT: TRUE					0.675			0.446
					-0.169			-0.2
Age: 55-65						-0.124		-0.269
						-0.187		-0.194
Age: 65+						-0.158		-0.431
						-0.203		-0.215
Path Stage: 3b							0.845	0.647
							-0.185	-0.203
Path Stage: 3a							1.839	1.389
							-0.204	-0.257
Path Stage: 4							1.069	1.075
							-0.459	-0.488
Observations	521	513	515	521	521	521	521	508
R^2	0.002	0.005	0.0001	0.099	0.027	0.001	0.127	0.171
Max. Possible R^2	0.98	0.98	0.979	0.98	0.98	0.98	0.98	0.98
Log Likelihood	-1,020.72	-1,006.22	-996.017	-994.057	-1,014.11	-1,020.88	-985.903	-940.834
Wald Test	1.070 (df =	2.670 (df = 3)	0.040 (df =	57.670	(df	15.880	(df = 1)	0.670 (df =	87.410	(df =	110.990	(df
LR Test	0.961 (df =	2.554 (df = 3)	0.040 (df =	54.294	(df	14.190	(df = 1)	0.659 (df =	70.602	(df =	95.471	(df =
Score (Logrank) Test	1.090 (df =	2.686 (df = 3)	0.040 (df =	66.672	(df	16.490	(df = 1)	0.673 (df =	107.851	(df	134.828	(df

Note: *p<0.1;**p<0.05;***p<0.01

Table S3: Univariate and multivariate cox proportional hazards regression analyses between PC clinical variables and time to biochemical recurrence. Related to Figure 1E.