

Supplemental Materials: Enhanced DNA Repair Pathway is Associated with Cell Proliferation and Worse Survival in Hepatocellular Carcinoma (HCC)

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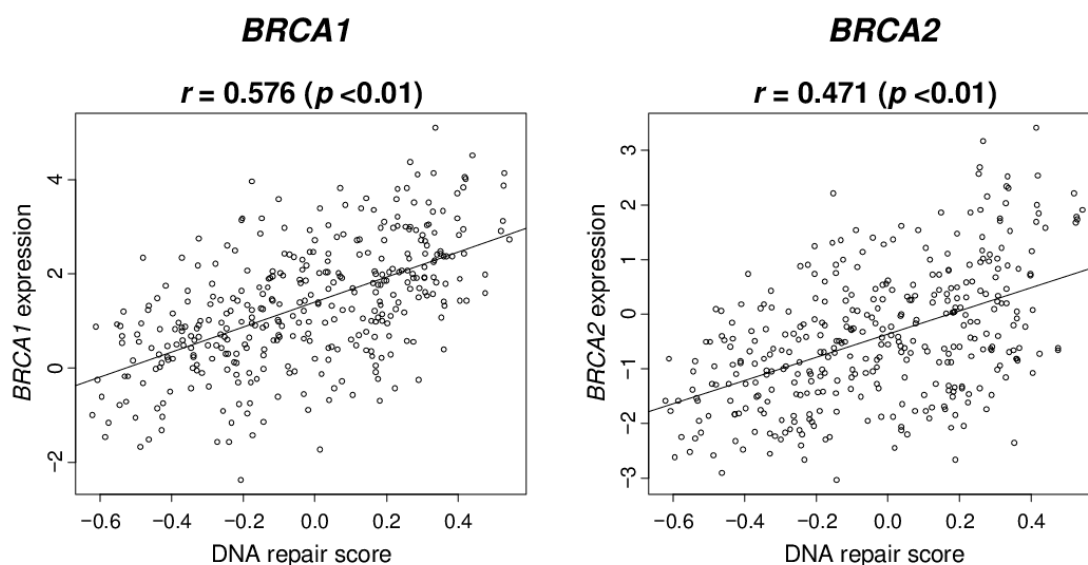


Figure S1. The correlation of the DNA repair score with expression of *BRCA1* and *BRCA2* genes in the TCGA cohort. Correlation plots of the DNA repair score with expression of the *BRCA1* and *BRCA2* genes. Spearman's rank correlation coefficient was used to calculate the p -value.

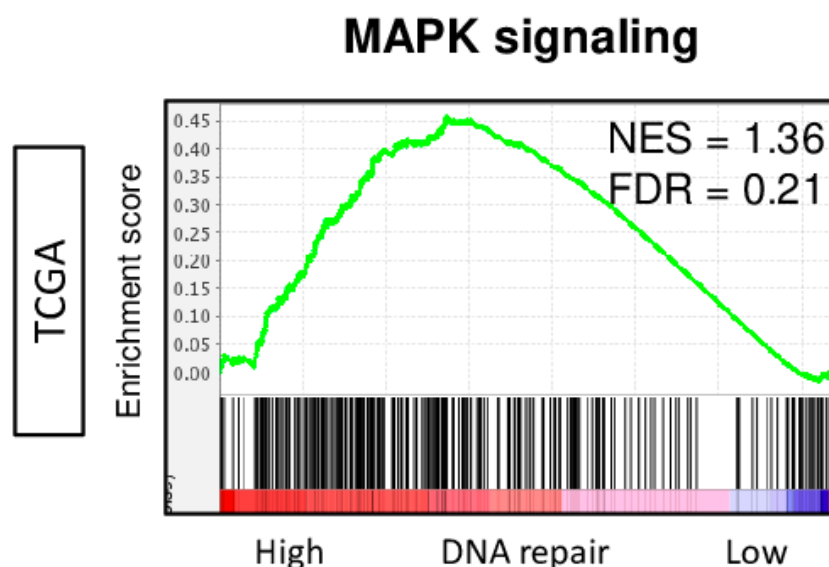


Figure S2. Gene set enrichment analysis (GSEA) of the KEGG MAPK signaling gene sets by high vs low DNA repair score of HCC in the TCGA cohort. Enrichment plots along with normalized enrichment score (NES) and false discovery rate (FDR) for the KEGG MAPK signaling gene set. An FDR of 0.25 was used to deem statistical Scheme 3. The correlation of the DNA repair score with drug sensitivity of Lenvatinib, Cabozantinib, Sorafenib, and Regorafenib in HCC cell lines. The correlation plots are between the DNA repair score and the level of drug sensitivity area under curve (AUC) of Lenvatinib, Cabozantinib, Sorafenib, and Regorafenib in HCC cell lines. Gene expression data of the HCC cell lines and response to drugs were obtained from the DepMap

portal, which were HEP3B217, HLF, HUH1, HUH7, JHH2, JHH4, JHH5, JHH6, JHH7, PLCPRF5, SKHEP1, SNU182, SNU387, SNU398, SNU423, SNU449, SNU475, SNU761, SNU878, and SNU886. Spearman correlation statistics were used for the analysis.

Table S1. Genes included in the Molecular Signatures Database (MSigDB) Hallmark DNA repair gene set.

Gene Symbol	Gene description
AAAS	aladin WD repeat nucleoporin
ADA	adenosine deaminase
ADCY6	adenylate cyclase 6
ADRM1	adhesion regulating molecule 1
AK1	adenylate kinase 1
AK3	adenylate kinase 3
APRT	adenine phosphoribosyltransferase
ARL6IP1	ADP ribosylation factor like GTPase 6 interacting protein 1
BCAM	basal cell adhesion molecule
BCAP31	B cell receptor associated protein 31
BOLA2	bolA family member 2
BRF2	BRF2 RNA polymerase III transcription initiation factor subunit
MPC2	mitochondrial pyruvate carrier 2
CANT1	calcium activated nucleotidase 1
CCNO	cyclin O
CDA	cytidine deaminase
CETN2	centrin 2
CLP1	cleavage factor polyribonucleotide kinase subunit 1
CMPK2	cytidine/uridine monophosphate kinase 2
NELFB	negative elongation factor complex member B
COX17	cytochrome c oxidase copper chaperone COX17
CSTF3	cleavage stimulation factor subunit 3
DAD1	defender against cell death 1
DCTN4	dynactin subunit 4
DDB1	damage specific DNA binding protein 1
DDB2	damage specific DNA binding protein 2
GSDME	gasdermin E
DGCR8	DGCR8 microprocessor complex subunit
DGUOK	deoxyguanosine kinase
DUT	deoxyuridine triphosphatase
EDF1	endothelial differentiation related factor 1
EIF1B	eukaryotic translation initiation factor 1B
AGO4	argonaute RISC component 4
ELL	elongation factor for RNA polymerase II
ERCC1	ERCC excision repair 1, endonuclease non-catalytic subunit
ERCC2	ERCC excision repair 2, TFIIH core complex helicase subunit
ERCC3	ERCC excision repair 3, TFIIH core complex helicase subunit
ERCC4	ERCC excision repair 4, endonuclease catalytic subunit
ERCC5	ERCC excision repair 5, endonuclease
ERCC8	ERCC excision repair 8, CSA ubiquitin ligase complex subunit
FEN1	flap structure-specific endonuclease 1
GMPR2	guanosine monophosphate reductase 2
GPX4	glutathione peroxidase 4
GTF2A2	general transcription factor IIF subunit 2
GTF2B	general transcription factor IIB
GTF2F1	general transcription factor IIF subunit 1
GTF2H1	general transcription factor IIH subunit 1
GTF2H3	general transcription factor IIH subunit 3
GTF2H5	general transcription factor IIH subunit 5
GTF3C5	general transcription factor IIIC subunit 5
GUK1	guanylate kinase 1

HCLS1	hematopoietic cell-specific Lyn substrate 1
HPRT1	hypoxanthine phosphoribosyltransferase 1
IMPDH2	inosine monophosphate dehydrogenase 2
ITPA	inosine triphosphatase
LIG1	DNA ligase 1
MPG	N-methylpurine DNA glycosylase
MRPL40	mitochondrial ribosomal protein L40
NCBP2	nuclear cap binding protein subunit 2
NFX1	nuclear transcription factor, X-box binding 1
NME1	NME/NM23 nucleoside diphosphate kinase 1
NME3	NME/NM23 nucleoside diphosphate kinase 3
NME4	NME/NM23 nucleoside diphosphate kinase 4
NPR2	natriuretic peptide receptor 2
NT5C	5', 3'-nucleotidase, cytosolic
NT5C3A	5'-nucleotidase, cytosolic IIIA
NUDT21	nudix hydrolase 21
NUDT9	nudix hydrolase 9
PCNA	proliferating cell nuclear antigen
PDE4B	phosphodiesterase 4B
PDE6G	phosphodiesterase 6G
PNP	purine nucleoside phosphorylase
POLA1	DNA polymerase alpha 1, catalytic subunit
POLA2	DNA polymerase alpha 2, accessory subunit
POLB	DNA polymerase beta
POLD1	DNA polymerase delta 1, catalytic subunit
POLD3	DNA polymerase delta 3, accessory subunit
POLD4	DNA polymerase delta 4, accessory subunit
POLE4	DNA polymerase epsilon 4, accessory subunit
POLH	DNA polymerase eta
POLL	DNA polymerase lambda
POLR1C	RNA polymerase I and III subunit C
POLR1D	RNA polymerase I and III subunit D
POLR2A	RNA polymerase II subunit A
POLR2C	RNA polymerase II subunit C
POLR2D	RNA polymerase II subunit D
POLR2E	RNA polymerase II subunit E
POLR2F	RNA polymerase II subunit F
POLR2G	RNA polymerase II subunit G
POLR2H	RNA polymerase II subunit H
POLR2I	RNA polymerase II subunit I
POLR2J	RNA polymerase II subunit J
POLR2K	RNA polymerase II subunit K
POLR3C	RNA polymerase III subunit C
POLR3GL	RNA polymerase III subunit G like
POM121	POM121 transmembrane nucleoporin
PRIM1	DNA primase subunit 1
RAD51	RAD51 recombinase
RAD52	RAD52 homolog, DNA repair protein
RAE1	ribonucleic acid export 1
RALA	RAS like proto-oncogene A
RBX1	ring-box 1
NELFE	negative elongation factor complex member E
REV3L	REV3 like, DNA directed polymerase zeta catalytic subunit
RFC2	replication factor C subunit 2
RFC3	replication factor C subunit 3
RFC4	replication factor C subunit 4
RFC5	replication factor C subunit 5
RNMT	RNA guanine-7 methyltransferase
RPA2	replication protein A2

RPA3	replication protein A3
RRM2B	ribonucleotide reductase regulatory TP53 inducible subunit M2B
SAC3D1	SAC3 domain containing 1
SDCBP	syndecan binding protein
SEC61A1	SEC61 translocon subunit alpha 1
SF3A3	splicing factor 3a subunit 3
SMAD5	SMAD family member 5
SNAPC4	small nuclear RNA activating complex polypeptide 4
SNAPC5	small nuclear RNA activating complex polypeptide 5
SRSF6	small nuclear RNA activating complex polypeptide 6
SSRP1	structure specific recognition protein 1
STX3	syntaxin 3
SUPT4H1	SPT4 homolog, DSIF elongation factor subunit
SUPT5H	SPT5 homolog, DSIF elongation factor subunit
SURF1	SURF1 cytochrome c oxidase assembly factor
TAF10	TATA-box binding protein associated factor 10
TAF12	TATA-box binding protein associated factor 12
TAF13	TATA-box binding protein associated factor 13
TAF1C	TATA-box binding protein associated factor, RNA polymerase I subunit C
TAF6	TATA-box binding protein associated factor 6
TAF9	TATA-box binding protein associated factor 9
TARBP2	TARBP2 subunit of RISC loading complex
ELOA	elongin A
NELFCD	negative elongation factor complex member C/D
ALYREF	Aly/REF export factor
TK2	thymidine kinase 2
TMED2	transmembrane p24 trafficking protein 2
TP53	tumor protein p53
TSG101	tumor susceptibility 101
TYMS	thymidylate synthetase
UMPS	uridine monophosphate synthetase
UPF3B	UPF3B regulator of nonsense mediated mRNA decay
USP11	ubiquitin specific peptidase 11
VPS28	VPS28 subunit of ESCRT-I
VPS37B	VPS37B subunit of ESCRT-I
VPS37D	VPS37D subunit of ESCRT-I
XPC	XPC complex subunit, DNA damage recognition and repair factor
ZNF707	zinc finger protein 707
ZNRD1	zinc ribbon domain containing 1
ZWINT	ZW10 interacting kinetochore protein

Table S2. Association between disease-specific survival and expression of multiple genes in the DNA repair pathway in the TCGA cohort. The Cox proportional hazards regression model with disease-specific survival was used in the analysis.

Gene	HR	95% CI		p
NME1	1.45	1.23	- 1.70	0.0000
SAC3D1	1.56	1.29	- 1.90	0.0000
NELFCD	1.61	1.28	- 2.02	0.0001
TAF9	1.52	1.24	- 1.88	0.0001
POLR2I	1.49	1.22	- 1.82	0.0001
ZWINT	1.26	1.12	- 1.41	0.0001
POLD1	1.36	1.15	- 1.59	0.0002
NT5C3A	1.41	1.17	- 1.69	0.0003
RAE1	1.50	1.20	- 1.86	0.0003
EDF1	1.44	1.18	- 1.76	0.0004
NT5C	1.38	1.15	- 1.65	0.0004
RFC5	1.37	1.15	- 1.64	0.0005
LIG1	1.34	1.13	- 1.58	0.0006

POLA1	1.30	1.12 -	1.52	0.0007
RPA3	1.43	1.16 -	1.76	0.0008
POLR1C	1.44	1.16 -	1.78	0.0008
RAD51	1.22	1.09 -	1.38	0.0009
DAD1	1.51	1.19 -	1.93	0.0009
RALA	1.46	1.16 -	1.82	0.0010
AAAS	1.53	1.18 -	1.96	0.0011
PCNA	1.32	1.12 -	1.57	0.0011
SUPT4H1	1.44	1.16 -	1.80	0.0012
TAF12	1.45	1.16 -	1.81	0.0012
UPF3B	1.35	1.12 -	1.62	0.0014
RFC4	1.28	1.10 -	1.49	0.0017
PRIM1	1.25	1.09 -	1.43	0.0019
GTF3C5	1.45	1.15 -	1.84	0.0019
FEN1	1.26	1.09 -	1.46	0.0020
TAF10	1.47	1.15 -	1.89	0.0020
ERCC3	1.39	1.13 -	1.72	0.0022
SSRP1	1.38	1.12 -	1.70	0.0024
RFC2	1.33	1.11 -	1.60	0.0025
DCTN4	1.41	1.13 -	1.77	0.0028
SUPT5H	1.42	1.13 -	1.78	0.0029
POLA2	1.31	1.10 -	1.57	0.0031
SF3A3	1.40	1.12 -	1.76	0.0035
NELFE	1.28	1.09 -	1.52	0.0035
SNAPC4	1.36	1.11 -	1.67	0.0035
ALYREF	1.28	1.08 -	1.51	0.0039
POLE4	1.29	1.08 -	1.53	0.0040
IMPDH2	1.29	1.08 -	1.54	0.0046
GTF2H1	1.38	1.10 -	1.73	0.0061
POLR2D	1.41	1.10 -	1.79	0.0062
ELOA	1.40	1.10 -	1.78	0.0062
ITPA	1.33	1.08 -	1.63	0.0063
POLR2J	1.33	1.08 -	1.64	0.0066
APRT	1.30	1.08 -	1.57	0.0066
NME3	1.30	1.08 -	1.57	0.0067
POLR3C	1.32	1.07 -	1.62	0.0081
POLB	1.26	1.06 -	1.50	0.0087
RFC3	1.21	1.05 -	1.40	0.0094
POLR2K	1.33	1.07 -	1.65	0.0103
TARBP2	1.33	1.07 -	1.64	0.0103
ERCC8	1.34	1.07 -	1.69	0.0110
POLR2H	1.30	1.06 -	1.59	0.0118
AK1	1.24	1.04 -	1.47	0.0144
RPA2	1.30	1.05 -	1.60	0.0146
POLD3	1.23	1.04 -	1.45	0.0156
TAF1C	1.27	1.04 -	1.54	0.0185
TYMS	1.15	1.02 -	1.29	0.0208
NELFB	1.31	1.04 -	1.65	0.0224
GTF2A2	1.33	1.04 -	1.70	0.0233
CSTF3	1.29	1.03 -	1.60	0.0241
GTF2H3	1.22	1.02 -	1.46	0.0258
CANT1	1.25	1.03 -	1.53	0.0264
ADCY6	1.20	1.02 -	1.42	0.0280
CETN2	1.25	1.02 -	1.52	0.0290
ERCC1	1.26	1.02 -	1.54	0.0300
TAF13	1.25	1.02 -	1.52	0.0317
ZNRD1	1.22	1.02 -	1.47	0.0333
NME4	1.18	1.01 -	1.38	0.0346
NUDT21	1.23	1.01 -	1.50	0.0370

ARL6IP1	1.21	1.01	-	1.45	0.0370
POLR3GL	1.23	1.01	-	1.49	0.0375
DGUOK	1.26	1.01	-	1.56	0.0378
SEC61A1	1.26	1.01	-	1.57	0.0430
POLL	1.29	1.01	-	1.65	0.0435
POLR2C	1.22	1.00	-	1.49	0.0447
TSG101	1.29	1.00	-	1.65	0.0458
STX3	1.15	1.00	-	1.33	0.0507
RBX1	1.25	1.00	-	1.56	0.0527
UMPS	1.25	1.00	-	1.57	0.0530
DGCR8	1.23	0.99	-	1.52	0.0615
ERCC2	1.22	0.99	-	1.49	0.0623
PNP	1.16	0.99	-	1.35	0.0664
DDB1	1.24	0.98	-	1.57	0.0671
POLR2G	1.22	0.98	-	1.52	0.0691
EIF1B	1.24	0.98	-	1.56	0.0713
NUDT9	1.20	0.98	-	1.47	0.0761
MRPL40	1.24	0.98	-	1.58	0.0769
NFX1	1.20	0.98	-	1.48	0.0787
GUK1	1.21	0.98	-	1.50	0.0815
TK2	1.21	0.98	-	1.50	0.0831
SRSF6	1.23	0.97	-	1.56	0.0839
BRF2	1.14	0.98	-	1.33	0.0902
DUT	1.16	0.97	-	1.38	0.0941
VPS28	1.18	0.97	-	1.42	0.0950
USP11	1.17	0.97	-	1.41	0.0956
TAF6	1.14	0.98	-	1.33	0.0974
RNMT	1.16	0.97	-	1.39	0.0975
ADRM1	1.22	0.96	-	1.54	0.1082
BCAP31	1.16	0.97	-	1.40	0.1121
POLR1D	1.19	0.96	-	1.46	0.1145
POLR2E	1.22	0.95	-	1.55	0.1156
ADA	1.13	0.97	-	1.31	0.1159
SMAD5	1.15	0.97	-	1.36	0.1195
ERCC5	1.19	0.95	-	1.48	0.1288
REV3L	1.12	0.97	-	1.30	0.1354
VPS37D	1.12	0.96	-	1.30	0.1526
MPC2	1.16	0.94	-	1.43	0.1553
POLR2F	1.23	0.92	-	1.63	0.1591
ZNF707	1.15	0.94	-	1.40	0.1662
GTF2F1	1.18	0.93	-	1.50	0.1718
HPRT1	1.12	0.95	-	1.33	0.1750
SNAPC5	1.18	0.93	-	1.48	0.1757
AK3	1.12	0.94	-	1.33	0.1955
RRM2B	1.13	0.94	-	1.35	0.1969
SURF1	1.16	0.93	-	1.44	0.2000
XPC	1.13	0.93	-	1.36	0.2092
TMED2	1.15	0.92	-	1.42	0.2145
GMPR2	1.15	0.92	-	1.44	0.2314
GTF2B	1.15	0.91	-	1.44	0.2425
GTF2H5	1.14	0.91	-	1.43	0.2643
HCLS1	0.92	0.80	-	1.06	0.2712
RAD52	1.11	0.92	-	1.34	0.2739
CLP1	1.14	0.90	-	1.45	0.2757
VPS37B	1.09	0.93	-	1.29	0.2772
POM121	1.07	0.94	-	1.22	0.2828
ELL	1.12	0.91	-	1.39	0.2859
POLH	1.08	0.92	-	1.26	0.3362
COX17	1.12	0.87	-	1.44	0.3697

CDA	1.04	0.95 -	1.14	0.4271
POLR2A	1.07	0.90 -	1.27	0.4525
GPX4	1.09	0.87 -	1.37	0.4604
BCAM	0.96	0.85 -	1.08	0.4949
NPR2	0.97	0.87 -	1.07	0.5532
GSDME	0.97	0.88 -	1.07	0.5842
NCBP2	1.06	0.85 -	1.33	0.5884
TP53	0.96	0.82 -	1.12	0.6096
DDB2	0.96	0.81 -	1.15	0.6707
CMPK2	1.03	0.91 -	1.16	0.6764
MPG	1.04	0.85 -	1.27	0.6964
ERCC4	1.03	0.88 -	1.20	0.7402
SDCBP	1.02	0.86 -	1.21	0.7935
AGO4	1.02	0.85 -	1.23	0.8148
POLD4	1.00	0.82 -	1.22	0.9801
PDE4B	1.00	0.89 -	1.12	0.9812
CCNO	1.00	0.94 -	1.07	0.9927

*CI, confidence interval; HR, hazard ratio.