

Supplementary Table 1

Source	Subtype	Sample No.	Variant Classification code																	Total	
			a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	q		r
Dulak_et.al	EAC	145	222	1047	210	509	371	208	93	146	19	2396	15003	884	17	686	5149	279	293	16	27548
TCGA-EAC	EAC	88	13	27	12	18	1002	325	0	158	28	160	16598	1299	12	48	5337	156	382	3	25578
ICGC-EAC	EAC	213	723	10874	281	2109	199	108	1	88	10	1475	13333	726	19	41	4669	1731	439	21	36847
ICGC-ESCC	ESCC	228	308	943	329	166	174	107	103	45	23	5006	12493	985	14	236	4624	333	281	18	26188
Lin_et.al	ESCC	20	1	1	2	2	25	14	0	17	2	9	950	92	2	8	4	0	28	2	1159
Sawada_et.al	ESCC	144	32	36	39	15	389	352	9	71	25	204	13691	1032	28	79	4996	135	327	37	21497
TCGA-ESCC	ESCC	97	20	18	19	6	532	255	0	141	19	117	12665	1073	22	44	3943	132	328	3	19337
Gao_et.al	ESCC	113	25	32	22	28	176	133	0	47	4	187	7125	586	13	71	2522	323	159	5	11458

Variant Classification	Code
3'Flank	a
3'UTR	b
5'Flank	c
5'UTR	d
Frame_Shift_Del	e
Frame_Shift_Ins	f
IGR	g
In_Frame_Del	h
In_Frame_Ins	i
Intron	j
Missense	k
Nonsense	l
Nonstop	m
RNA	n
Silent	o
Splice_Region	p
Splice_Site	q
Translation_Start_Site	r

Supplementary Table 2

Sample ID	Call Status	Purity	Ploidy	Genome doublings	Coverage for 80% power	Cancer DNA fraction	Subclonal genome fraction
TCGA.L5.A8NM	called	1	7.96	0	42	1	0
TCGA.L5.A4OP	called	0.69	7.26	0	43	0.89	0
TCGA.L5.A8NI	called	0.51	7.29	0	49	0.79	0
TCGA.M9.A5M8	called	0.61	7.2	0	45	0.85	0.01
TCGA.IG.A7DP	called	0.65	7.87	0	48	0.88	0.07
TCGA.L5.A4OE	called	0.62	5.51	0	35	0.82	0.03
TCGA.L5.A43C	called	0.63	7.9	0	49	0.87	0.01
TCGA.R6.A8WC	called	0.68	5.08	0	30	0.84	0.03
TCGA.L5.A4OI	called	0.81	2.14	0	10	0.82	0.04
TCGA.L5.A4OJ	called	0.67	8.07	0	49	0.89	0.01
TCGA.S8.A6BV	called	0.58	3.98	0	26	0.73	0.12
TCGA.VR.AA4D	called	0.56	7.68	0	50	0.83	0.04
TCGA.JY.A938	called	0.43	6.55	0	49	0.71	0.01
TCGA.L5.A4OT	called	0.63	4.82	0	30	0.8	0.02
TCGA.IG.A4QS	called	0.73	6.68	0	39	0.9	0.02
TCGA.L5.A4OH	called	0.55	6.98	0	46	0.81	0.02
TCGA.JY.A6FH	called	0.48	7.7	0	53	0.78	0.01
TCGA.V5.A7RB	called	0.34	6.37	0	55	0.62	0.06
TCGA.R6.A6Y2	called	0.5	9.6	0	63	0.83	0.07
TCGA.L5.A4OG	called	0.64	4.73	0	29	0.81	0.04
TCGA.R6.A8W8	called	0.56	6.33	0	42	0.8	0.02
TCGA.JY.A93E	called	0.71	4.67	0	26	0.85	0.03
TCGA.JY.A939	called	0.4	7.03	0	54	0.7	0
TCGA.L5.A88T	called	0.43	4.23	0	36	0.61	0.05
TCGA.L5.A4OO	called	0.4	6.27	0	49	0.68	0.01
TCGA.2H.A9GQ	called	0.59	9.13	0	57	0.87	0.04
TCGA.2H.A9GJ	called	0.5	7.99	0	54	0.8	0.01
TCGA.VR.A8EQ	called	0.62	6.1	0	38	0.83	0.03
TCGA.L5.A8NW	called	0.51	5.29	0	38	0.73	0.03
TCGA.L5.A43M	called	0.69	6.33	0	38	0.88	0.02
TCGA.R6.A6L6	called	0.56	8.34	0	53	0.84	0.01
TCGA.R6.A6L4	called	0.72	4.75	0	26	0.86	0.09
TCGA.R6.A6XG	called	0.38	7.57	0	58	0.7	0.02
TCGA.L5.A8NU	called	0.57	8.82	0	56	0.85	0.02
TCGA.RE.A7BO	called	0.59	9.88	0	61	0.88	0.03
TCGA.L5.A8NJ	called	0.76	2.82	0	14	0.82	0.12
TCGA.L5.A88Y	called	0.49	6.51	0	46	0.76	0.02
TCGA.L5.A8NL	called	0.49	7.24	0	50	0.78	0.01
TCGA.R6.A8W5	called	0.34	5.09	0	48	0.57	0.03
TCGA.ZR.A9CJ	called	0.66	6.56	0	40	0.86	0.03
TCGA.L7.A6VZ	called	0.68	7.64	0	46	0.89	0.04
TCGA.L5.A4OS	called	0.42	6.48	0	50	0.7	0.03
TCGA.L5.A43I	called	0.44	7.16	0	52	0.74	0.02
TCGA.L5.A88V	called	0.62	9.08	0	56	0.88	0.05
TCGA.L5.A8NE	called	0.39	6.79	0	53	0.68	0.02
TCGA.X8.AAAR	called	0.63	8.61	0	53	0.88	0.01
TCGA.JY.A6FB	called	0.44	8.85	0	61	0.78	0.01
TCGA.R6.A8WG	called	0.45	8.32	0	58	0.77	0.01
TCGA.L5.A43E	called	0.42	7.59	0	56	0.73	0.01
TCGA.R6.A6Y0	called	0.3	7.71	0	67	0.62	0.01
TCGA.L5.A8NT	called	0.54	4.36	0	31	0.72	0.07
TCGA.L5.A4OU	called	0.67	6.04	0	37	0.86	0.04
TCGA.JY.A6F8	called	0.48	7.89	0	54	0.79	0.04
TCGA.L5.A8NR	called	0.83	7.58	0	42	0.95	0.03
TCGA.JY.A93D	called	0.4	8.23	0	61	0.73	0.01
TCGA.2H.A9GN	called	0.48	5.73	0	42	0.72	0.03
TCGA.R6.A6DQ	called	0.65	8.7	0	53	0.89	0.03
TCGA.L5.A893	called	0.5	9.82	0	64	0.83	0
TCGA.V5.AASW	called	0.58	8.9	0	56	0.86	0.02
TCGA.L5.A4OF	called	0.53	9.32	0	60	0.84	0
TCGA.L5.A8NS	called	0.47	8.04	0	56	0.78	0.01
TCGA.2H.A9GH	called	0.52	6.61	0	45	0.78	0.03
TCGA.L5.A4OX	called	0.41	9.03	0	65	0.76	0.03
TCGA.JY.A93C	called	0.62	9.85	0	60	0.89	0.08
TCGA.2H.A9GO	called	0.4	8.55	0	63	0.74	0.02
TCGA.R6.A6KZ	called	0.42	9.27	0	65	0.77	0.01
TCGA.L5.A4OW	called	0.51	7.78	0	52	0.8	0.02
TCGA.2H.A9GR	called	0.37	5.71	0	49	0.63	0.02
TCGA.Q9.A6FW	called	0.62	4.03	0	24	0.77	0.13
TCGA.2H.A9GM	called	0.54	5.86	0	40	0.77	0.06
TCGA.L5.A8NF	called	0.61	7.93	0	50	0.86	0.04
TCGA.R6.A6DN	called	0.6	7.65	0	48	0.85	0.04
TCGA.L5.A8NG	called	0.44	8.76	0	61	0.78	0.01

TCGA.L5.A8NV	called	0.35	7.92	0	63	0.68	0
TCGA.L5.A8NN	called	0.45	9.29	0	64	0.79	0.01
TCGA.L5.A4OR	called	0.58	8.19	0	52	0.85	0.05
TCGA.V5.A7RE	called	0.44	5.3	0	42	0.67	0.05
TCGA.L5.A8NH	called	0.43	6.74	0	50	0.72	0.03
TCGA.2H.A9GL	called	0.51	9.22	0	60	0.83	0.04
TCGA.L5.A4ON	called	0.52	4.93	0	35	0.72	0.14
TCGA.V5.AASX	called	0.44	8.62	0	60	0.77	0.01
TCGA.IC.A6RE	called	0.36	8.81	0	67	0.71	0.01
TCGA.2H.A9GI	called	0.39	8.4	0	62	0.73	0.03
TCGA.2H.A9GK	called	0.42	6.48	0	50	0.7	0.02
TCGA.IG.A4QT	called	0.64	3.96	0	21	0.78	0.02
TCGA.IC.A6RF	called	0.6	6.15	0	40	0.82	0
TCGA.JY.A93F	called	0.91	5.98	0	31	0.97	0
TCGA.L5.A88W	called	0.62	4.94	0	31	0.8	0.02
TCGA.VR.AA4G	called	0.62	6.81	0	43	0.85	0.01
TCGA.XP.A8T7	called	0.53	8.72	0	57	0.83	0
TCGA.JY.A6FG	called	0.56	4.07	0	28	0.72	0.05
TCGA.LN.A49N	called	0.52	6.69	0	46	0.78	0.16
TCGA.IG.A97I	called	0.59	5.01	0	33	0.78	0.02
TCGA.IG.A6QS	called	0.59	9.42	0	59	0.87	0.04
TCGA.IG.A3I8	called	0.46	7.41	0	52	0.76	0.02
TCGA.JY.A6FD	called	0.6	8.79	0	54	0.87	0
TCGA.IG.A3YA	called	0.37	6.07	0	51	0.64	0.02
TCGA.IG.A5B8	called	0.57	5.82	0	38	0.79	0.01
TCGA.LN.A49O	called	0.53	8.17	0	54	0.82	0.01
TCGA.LN.A4A2	called	0.55	8.27	0	53	0.83	0.01
TCGA.LN.A4A6	called	0.69	5.1	0	30	0.85	0.04
TCGA.KH.A6WC	called	0.52	7.04	0	48	0.79	0
TCGA.LN.A4A8	called	0.54	3.97	0	28	0.7	0.07
TCGA.LN.A4MR	called	0.65	4.07	0	21	0.79	0.08
TCGA.LN.A4A1	called	0.5	8.21	0	55	0.8	0.03
TCGA.LN.A9FO	called	0.61	8.62	0	53	0.87	0.01
TCGA.LN.A4A5	called	0.59	4.73	0	31	0.77	0.04
TCGA.V5.AASV	called	0.6	4.62	0	30	0.78	0.04
TCGA.LN.A49M	called	0.51	7.85	0	53	0.8	0.01
TCGA.IG.A3YC	called	0.49	6.96	0	48	0.77	0.01
TCGA.VR.A8Q7	called	0.48	5.82	0	42	0.73	0.02
TCGA.L5.A8NK	called	0.65	8.55	0	52	0.89	0.01
TCGA.VR.AA7B	called	0.61	8.48	0	52	0.87	0.04
TCGA.L5.A88S	called	0.68	7.7	0	46	0.89	0.02
TCGA.IG.A51D	called	0.61	5.22	0	33	0.8	0.05
TCGA.LN.A4A4	called	0.58	6	0	39	0.81	0.04
TCGA.VR.AA7D	called	0.69	5.12	0	30	0.85	0.05
TCGA.Z6.A8JD	called	0.57	8.2	0	52	0.84	0.02
TCGA.V5.A7RC	called	0.6	8.92	0	55	0.87	0.05
TCGA.IG.A625	called	0.65	7.56	0	46	0.87	0.02
TCGA.IG.A8O2	called	0.55	7.32	0	48	0.81	0.01
TCGA.VR.AA7I	called	0.69	5.17	0	31	0.85	0.06
TCGA.LN.A5U7	called	0.77	7.18	0	41	0.92	0.06
TCGA.LN.A7HW	called	0.61	8.29	0	52	0.86	0.04
TCGA.LN.A8I1	called	0.53	7.77	0	51	0.81	0.03
TCGA.S8.A6BW	called	0.48	7.38	0	51	0.77	0.03
TCGA.LN.A49L	called	0.67	7.36	0	44	0.88	0.03
TCGA.LN.A49U	called	0.82	5.06	0	26	0.92	0.06
TCGA.LN.A7HV	called	0.42	8.9	0	63	0.76	0.01
TCGA.LN.A8I0	called	0.54	6.59	0	44	0.8	0.02
TCGA.LN.A5U5	called	0.68	5.14	0	31	0.84	0.06
TCGA.Q9.A6FU	called	0.74	4.68	0	25	0.87	0.1
TCGA.LN.A7HX	called	0.43	7.5	0	55	0.74	0.02
TCGA.L5.A43H	called	0.42	6.95	0	52	0.71	0.01
TCGA.VR.A8ER	called	0.46	9.51	0	64	0.8	0.07
TCGA.XP.A8T8	called	0.68	7.73	0	46	0.89	0.03
TCGA.Z6.AAPN	called	0.82	6.75	0	38	0.94	0.03
TCGA.IG.A3Y9	called	0.45	6.69	0	49	0.73	0.01
TCGA.L5.A88Z	called	0.57	5.8	0	38	0.79	0.05
TCGA.IG.A50L	called	0.54	7.81	0	51	0.82	0.02
TCGA.XP.A8T6	called	0.41	7.58	0	56	0.72	0.02
TCGA.LN.A49W	called	0.63	5.78	0	36	0.83	0.04
TCGA.LN.A49K	called	0.5	8.23	0	55	0.8	0.05
TCGA.VR.A8EY	called	0.6	4.61	0	30	0.77	0.16
TCGA.VR.A8EO	called	0.62	7.81	0	48	0.87	0.06
TCGA.LN.A7HZ	called	0.64	8.22	0	50	0.88	0.04
TCGA.LN.A49P	called	0.81	5.28	0	28	0.92	0.08
TCGA.LN.A49X	called	0.46	7.39	0	52	0.76	0.01
TCGA.LN.A4A9	called	0.53	4.63	0	33	0.72	0.08
TCGA.LN.A9FR	called	0.43	9.1	0	64	0.78	0.01
TCGA.VR.A8EX	called	0.47	8.25	0	57	0.78	0.02
TCGA.LN.A49Y	high non-clonal	0.87	3.77	0	17	0.93	0.23

TCGA.L5.A43J	called	0.42	6.85	0	51	0.72	0.08
TCGA.VR.A8FP	called	0.58	5.03	0	33	0.78	0.05
TCGA.L5.A8NQ	called	0.63	9.58	0	58	0.89	0.06
TCGA.L5.A4OM	called	0.72	5.24	0	30	0.87	0.1
TCGA.LN.A4A3	called	0.62	8.95	0	55	0.88	0.02
TCGA.2H.A9GF	called	0.46	9.01	0	62	0.79	0.04
TCGA.LN.A9FQ	called	0.55	7.84	0	51	0.83	0.04
TCGA.L7.A56G	called	0.61	8.48	0	52	0.87	0.03
TCGA.LN.A7HY	called	0.48	7.26	0	51	0.77	0.04
TCGA.VR.A8ET	called	0.43	7.63	0	56	0.74	0.01
TCGA.VR.A8EZ	called	0.5	8.79	0	58	0.82	0.02
TCGA.IG.A5S3	called	0.87	6.95	0	38	0.96	0.05
TCGA.IG.A3YB	called	0.53	7.91	0	52	0.81	0.02
TCGA.JY.A6FE	called	0.39	7.54	0	58	0.71	0.04
TCGA.JY.A6FA	called	0.58	8.91	0	56	0.86	0.08
TCGA.LN.A49S	called	0.49	8.88	0	59	0.81	0.02
TCGA.LN.A8HZ	called	0.46	7.22	0	51	0.75	0.01
TCGA.IG.A97H	called	0.53	7.94	0	52	0.82	0.03
TCGA.VR.A8EU	called	0.47	7.35	0	52	0.77	0.03
TCGA.IG.A3QL	called	0.47	6.03	0	44	0.73	0.06
TCGA.VR.A8EW	called	0.6	7.24	0	46	0.84	0.03
TCGA.LN.A49R	called	0.53	7.1	0	47	0.8	0.02
TCGA.IG.A4P3	called	0.45	6.88	0	50	0.73	0.02
TCGA.LN.A49V	called	0.69	4.82	0	28	0.84	0.17
TCGA.Z6.A8JE	called	0.49	8.02	0	55	0.79	0.03
TCGA.LN.A4MQ	called	0.6	8.88	0	55	0.87	0.07
TCGA.LN.A5U6	called	0.49	7.48	0	51	0.78	0.05
TCGA.Z6.A9VB	called	0.45	8.57	0	59	0.78	0.05
TCGA.LN.A9FP	called	0.47	9.53	0	64	0.81	0

Supplementary Table 3

## ESCC

Signature	ATM	CUL3	CDKN2A	TP53	MLL2	NOTCH1	NFE2L2	ZNF750	FAT1	PIK3CA	EP300	MLL3	RB1	FBXW7	KDM6A	PTEN	AJUBA	TGFBR2	ZFP36L2	PTCH1
Signature 17	NA	NA	0.466	0.873	NA	0.765	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.222	NA	NA	NA	NA
Signature 1	0.980	0.907	0.542	0.571	0.941	0.025	0.923	0.985	0.292	0.534	0.724	0.769	0.995	0.481	0.818	0.698	0.836	0.691	0.859	0.105
APOBEC	0.813	0.865	0.949	0.394	0.008	0.685	0.848	0.000	0.340	0.006	0.466	0.024	0.042	0.681	0.275	0.451	0.285	0.910	0.520	0.985
Signature 4-like	NA	NA	0.877	0.996	NA	NA	0.849	0.961	0.958	NA	NA	0.840	0.830	NA	0.784	NA	NA	NA	NA	NA
Signature 16-like	0.424	0.317	0.284	0.131	0.885	0.517	0.252	0.606	0.839	0.915	0.190	0.699	0.474	0.605	0.346	0.897	0.138	0.385	0.833	0.465
Signature-A	0.002	0.326	0.205	0.515	0.184	0.756	0.252	0.869	0.711	0.200	0.894	0.764	0.933	0.222	0.903	0.723	0.818	0.108	0.636	0.265

## EAC

Signature	ARID1A	CDKN2A	DOCK2	PCDH18	SMAD4	SMARCA4	ATM	PIK3CA	FBXW7	KRAS	PBRM1	EPHA2	CTNNB1	C6orf114	SEMA5A	PGCP	TGFBR2	PTEN
Signature 17	0.959	0.985	0.046	0.000	1.000	0.846	0.891	0.759	0.631	0.631	0.987	0.359	0.645	0.833	0.178	0.851	0.647	0.885
Signature 1	0.316	0.124	0.927	0.980	0.561	0.254	0.896	0.606	0.639	0.148	0.305	0.812	0.826	0.612	0.878	0.443	0.844	0.417
APOBEC	0.573	NA	NA	NA	0.425	NA	NA	0.012	NA	NA	0.050	NA	NA	NA	0.402	NA	0.233	NA
Signature 4-like	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Signature 16-like	NA	NA	NA	NA	0.425	NA	NA	NA	NA	NA	NA	NA	NA	0.219	0.402	NA	NA	0.185
Signature-A	0.249	0.098	0.272	0.948	0.052	0.090	0.005	0.167	0.119	0.858	0.821	0.712	0.071	NA	0.460	0.740	0.368	NA

P value was determined by enrichment analysis (See methods) against all SMGs. Genes associated with DNA damage repair pathway were also included in this analysis.

Supplementary Table 4

Gene	Pooled siRNA	Sequence
CUL3	Sequence-1	UAAACAGCAUUUGGACCUUCUGAA
	Sequence-2	UGGAUGAAUUCAGGCAACAUUACA
	Sequence-3	CCCAGGUCUUCAGUGUUGAUGUAAA
	Sequence-4	UGUAGAUUUGCCUGAAUUCAUCCA
ZFP36L2	Sequence-1	CCGCCUUCUACGAUGUCGACUUCUU
	Sequence-2	GCCUUCUACGAUGUCGACUUCUUGU
	Sequence-3	GGAAGUAGUUUGAGGAAACAUCCAU
	Sequence-4	AUAGGAUGUCCUCAACUACUCC
PTCH1	Sequence-1	GAGGACGAGUAAGUCGUAUUAAA
	Sequence-2	ACAGGCAGUGGAAUUGGAAAUUU
	Sequence-3	CCCUGCAGACCAUGUUCAGUUAAU
	Sequence-4	UUUAAUUCACGACUUCUCGUCCUC
ATF5	Sequence-1	UCCAGUACGUCAAGGACCUUCUUAU
	Sequence-2	UCAAGGACCUUCUACGAGGUUUA
	Sequence-3	AGGACCUUCUACGAGGUUUAACA
	Sequence-4	AUGAGCAGGUCCUUGACGUACUGGA

Gene	Individual siRNA	Sequence
CUL3	Sequence-1	GGAGCAAGGUAAAGCUCUUTT
ZFP36L2	Sequence-1	GCCUUCUACGAUGUCGACUTT

Gene	PCR primers	Sequence
ATF5	Forward	GCTCGTAGACTATGGGAAACTC
	Reverse	AATCAACTCGCTCAGTCATCC
ZFP36L2	Forward	TGCGGGATCCAGAAACATG
	Reverse	TGTTCAGGTTGAGGTTGGC
CUL3	Forward	AGGTTCTACTTAGCCAACACAG
	Reverse	ACCTCCAACCAACTTCAG
PTCH1	Forward	TCTTGGTGTGGTGTGGATG
	Reverse	ATTGCTGATGGACGTGAGG
PRDX1	Forward	AGTGATTGGTGCTTCTGTGG
	Reverse	ACCCATAATCTGAGCAATG
ABCC3	Forward	CCTTTCTGTCTACTCTCTTG
	Reverse	CGCCTCTGTCTGTCTTG
ZFP36L2	Cloning-F-HindIII	CCCAAGCTTATGTCGACCACTTCTG
	Cloning-R-EcoRI	CCGGAATCCAAGTCGCGGAGATGGA