Supplementary Data

Table S1. ctDNA studies performed in early-stage tumors

Reference	Cancer type	Samples	Detection approach	Target	Expected mutations in ctDNA	Detected mutations in ctDNA	Range of mutant allelic fraction detected	Clinical outcome
Bettegowda *et al., Sci Trans Med* 2014	bladder, breast, colorectal, endometrial, head and neck, gastroesophageal, melanoma, non-small cell lung, pancreatic ductal	182	dPCR	panel of genes	variable**	40%-60%	1,1-22000 mutant fragments/5mL	NE
Sausen *et al., Nat Commun* 2015	pancreatic ductal adenocarcinoma	51	dPCR	*KRAS*	90%*	43%	0.01%-0.52%	higher risk of relapse in patients with detectable ctDNA at diagnosis
Beaver *et al., Clin Can Res* 2014	breast cancer	29	dPCR	*PIK3CA*	52%**	48%	0.01%-2.99%	NE
García-Mutillas *et al., Sci Trans Med* 2015	breast cancer	55	dPCR	panel of genes	76%**	53%	0.05%-0.8%	ctDNA detection at baseline, not predictive of disease-free survival. ctDNA abundance at baseline not associated with early relapse
Jamal-Hanjani *et al., Ann Oncol* 2016	lung adenocarcinoma and squamous cell carcinoma	4	multiplex PCR-NGS	panel of SNVs	37 SNVs**	16 SNVs(43%)	0.15–23.25%	NE

* Based on previous studies
** Based on tumor mutations
NE Not evaluated
§ According to concentration of mutations/ml

Table S2. Overview of the amount of cfDNA extracted per sample, and the on-target median coverage for the two independent libraries

Sample type	ID *TP53* mutation	ID Sample	ng DNA	Coverage - Lib1	Coverage - Lib2
Russian cases	SCLC-1	RS113010	11	6367	7966
Russian cases	SCLC-2	RS1131050	11	7812	7938
Russian cases	SCLC-3	RS1131091	15	7551	7856
Russian cases	SCLC-4	RS1131095	36	7525	7685
Russian cases	SCLC-5	RS1131107	15	7641	7585
Russian cases	SCLC-6	RS113338	11	7814	7900
Russian cases	SCLC-7	RS113340	11	5875,5	7963,5
Russian cases	SCLC-8	RS113475	38	7948	7783
Russian cases	SCLC-9	RS113688	11	7240	7910,5
Russian cases	SCLC-10	RS113697	37	7458	7886
Russian cases	SCLC-11	RS113725	15	7371	7242
Russian cases	SCLC-12	RS113811	13	7251	5069
Russian cases	SCLC-13	RS113989	18	7317	6231
Russian cases	SCLC-14	RS122064	234	7645	7946
Russian cases	SCLC-15	RS1221195	26	7281	7867
Russian cases	SCLC-16	RS122406	13	7917	7958
Russian cases	SCLC-17	RS122490	16	7818	7903
Russian cases	SCLC-18	RS122512	12	7670	7943
Russian cases	SCLC-19	RS122540	22	7707	7957
Russian cases	SCLC-20	RS122600	8	7873	7940
Russian cases	SCLC-21	RS122639	11	7628	7945
Russian cases	SCLC-22	RS122735	10	7123	7823
Russian cases	SCLC-23	RS122805	10	7675,5	7087
Russian cases	SCLC-24	RS122895	21	7012	7643
Russian cases	SCLC-25	RS122580	66	7554	7928
Russian cases	.	RS113004	11	6505	7927
Russian cases	.	RS1131153	7	7718	7957
Russian cases	.	RS1131172	9	7861	7957
Russian cases	.	RS113202	19	7633	7936
Russian cases	.	RS113275	8	7814	7950
Russian cases	.	RS113378	8	7899	7956
Russian cases	.	RS113484	8	7958	7947
Russian cases	.	RS113486	15	7502	7689
Russian cases	.	RS113628	7	7931	7931
Russian cases	.	RS122055	11	7467	7937
Russian cases	.	RS122058	8	7710	7832,5
Russian cases	.	RS1221008	40	7693	7930
Russian cases	.	RS1221053	9	7497	7950
Russian cases	.	RS122235	15	7916	7825
Russian cases	.	RS122246	12	7802	7577
Russian cases	.	RS122261	16	7398	7744
Russian cases	.	RS122277	27	7472	7924
Russian cases	.	RS122389	26	7849	7945
Russian cases	.	RS122752	15	7579	7597
Russian cases	.	RS122753	16	7428	7917
Russian cases	.	RS122762	11	7652	6248
Russian cases	.	RS122837	11	7526	7170
Russian cases	.	RS122927	31	7320	7156,5
Russian cases	.	RS122972	34	7772	3256
Russian cases	.	RS152032	23	6523	6932
Russian cases	.	RS152045	29	7610	7919
Replication controls	ARG-1	151485	402	7319	7801
Replication controls	ARG-2	151486	689	7590	7509
Replication controls	ARG-3	151496	198	7338	7016
Replication controls	ARG-4	151618	611	7898	7846
Replication controls	CRE-5	110087	96	7983	7542
Replication controls	CRE-6	110328	34	7985	1658
Replication controls	ITA-7	410146	17	7854	6253
Replication controls	ITA-8	420211	79	7916	6108
Replication controls	ITA-9	420232	988	7949	3991
Replication controls	ITA-10	430239	52	7964	7802
Replication controls	ITA-11	420261	11	7648,5	5463,5
Replication controls	.	151387	617	7455	7549
Replication controls	.	151489	339	7058	6016
Replication controls	.	110093	69	7976	7777
Replication controls	.	110138	52	7924	7946
Replication controls	.	110165	115	7957	7962
Replication controls	.	110229	33	7894	7278
Replication controls	.	110291	205	7982	5971
Replication controls	.	110294	28	7977	5882
Replication controls	.	110301	58	7974	2131,5
Replication controls	.	110309	85	7982	5179
Replication controls	.	110337	18	7979	3304
Replication controls	.	110353	69	7939	7884
Replication controls	.	110380	88	7983	7941
Replication controls	.	110407	58	1777	7647
Replication controls	.	151335	597	7180	7793
Replication controls	.	151340	288	7703	7626
Replication controls	.	151349	267	7076	7231
Replication controls	.	151351	780	1069	3930
Replication controls	.	151357	787	5174	3871
Replication controls	.	151370	186	6747	5535
Replication controls	.	151382	250	7151	6747
Replication controls	.	151396	69	7724	7202
Replication controls	.	151423	558	7765	7803
Replication controls	.	151439	2279	7464	7132
Replication controls	.	151450	442	7609	7783
Replication controls	.	151465	706	6760	5345
Replication controls	.	151474	634	7246	7448
Replication controls	.	151475	1254	7733	7798
Replication controls	.	151482	3333	4860	6240
Replication controls	.	151506	938	7350	7682
Replication controls	.	151509	558	7660	7726
Replication controls	.	151514	644	7745	7337
Replication controls	.	151522	598	7377	6582
Replication controls	.	151523	773	7433	7025
Replication controls	.	151535	422	6895	6950
Replication controls	.	151542	816	7085	7310
Replication controls	.	151558	447	7126	7000
Replication controls	.	151578	867	7459	7417
Replication controls	.	151581	714	6850	6306
Replication controls	.	151591	700	7002	7451
Replication controls	.	151592	217	6904	6060
Replication controls	.	151596	534	7258	7613
Replication controls	.	151602	5077	7503	7421
Replication controls	.	151607	195	4076	7255
Replication controls	.	151617	110	7405	7370
Replication controls	.	151624	207	7519	7138
Replication controls	.	151628	144	7308	7553
Replication controls	.	310012	12	7882	5290,5
Replication controls	.	310037	83	7844	7532
Replication controls	.	310042	2880	7104	3189
Replication controls	.	310052	1047	7597	6694
Replication controls	.	310057	191	7904	7536
Replication controls	.	310233	14	7870,5	6591
Replication controls	.	310257	14	7771	4598
Replication controls	.	310492	14	7905	6830
Replication controls	.	310526	170	7471	6050
Replication controls	.	410047	48	7871	4533
Replication controls	.	410113	11	7921,5	4818,5
Replication controls	.	410129	8	7896	5907
Replication controls	.	410157	40	7874	7377
Replication controls	.	410158	9	1793	4685,5
Replication controls	.	410198	9	6104	7022,5
Replication controls	.	410207	31	2635	6665
Replication controls	.	410240	17	7853	4650,5
Replication controls	.	410274	20	7955	4627
Replication controls	.	410285	8	7957	4517
Replication controls	.	410295	11	7895	6140
Replication controls	.	410297	8	7918	6040
Replication controls	.	420045	2442	7207	3338
Replication controls	.	420158	66	7746	5166,5
Replication controls	.	420233	1364	7818	5614
Replication controls	.	420265	22	7858	6473,5
Replication controls	.	420271	22	7658	6314
Replication controls	.	420301	918	7856	5337
Replication controls	.	420314	1553	7168	5847
Replication controls	.	420322	25	7956	5881,5
Replication controls	.	430114	21	7880	4687
Replication controls	.	430185	21	7810,5	3347,5
Replication controls	.	430191	21	7524	3642
Replication controls	.	430217	15	7875	6248
Replication controls	.	430240	15	7866	5934,5
Replication controls	.	430268	19	7485	4457
Replication controls	.	430274	17	7615	5906
Replication controls	.	430287	22	7938	6107,5
Replication controls	.	430289	10	7608,5	4956
Replication controls	.	430314	10	7924	7602
Replication controls	.	430318	299	7463	7820,5
Replication controls	.	430348	25	7931	6108
Replication controls	.	430365	28	7525	4927,5
Replication controls	.	430382	14	7738	4897
Replication controls	.	430403	11	7906	5675
Russian controls	MLT-1	RS132307	11	10093	27508
Russian controls	MLT-2	RS132327	15	23270	28881
Russian controls	MLT-3	RS130392	12	19870	36078
Russian controls	MLT-4	RS131040	37	15671	18178
Russian controls	MLT-5	RS131247	12	7196	29472
Russian controls	MLT-6	RS131302	21	27661	40009
Russian controls	MLT-7	RS131351	1466	5352	5519
Russian controls	MLT-8	RS131357	12	5264	21976
Russian controls	MLT-9	RS131425	18	7245	13462
Russian controls	MT-10	RS131466	48	8344	32265
Russian controls	MLT-11	RS131654	25	24465	27594
Russian controls	MLT-12	RS131687	12	5829	18801
Russian controls	MLT-13	RS131825	11	23519	10991
Russian controls	MLT-14	RS133194	13	22722	13538
Russian controls	.	RS131337	41	10491	8586
Russian controls	.	RS131573	12	10920	11468
Russian controls	.	RS130020	42	7001	13934
Russian controls	.	RS130021	45	17247	22167
Russian controls	.	RS130023	48	10973	15686
Russian controls	.	RS130093	14	6471	6492
Russian controls	.	RS130095	27	8687	6104
Russian controls	.	RS130120	15	17319	7445
Russian controls	.	RS130146	14	12464	7622
Russian controls	.	RS130200	13	16728	10885
Russian controls	.	RS130231	13	16015	17143
Russian controls	.	RS130269	20	17662	7591
Russian controls	.	RS130285	25	7854	6625
Russian controls	.	RS130294	426	10494	25809
Russian controls	.	RS130297	44	5225	9890
Russian controls	.	RS130318	100	7284	14488
Russian controls	.	RS130345	78	5822	8446
Russian controls	.	RS130480	31	13230	5666
Russian controls	.	RS130486	19	6543	8976
Russian controls	.	RS130492	21	9215	8771
Russian controls	.	RS130517	12	10844	5922
Russian controls	.	RS130518	19	13060	7333
Russian controls	.	RS130551	17	8464	9139
Russian controls	.	RS130558	24	7775	6955
Russian controls	.	RS130578	52	10910	35303
Russian controls	.	RS130586	26	7447	8310
Russian controls	.	RS130587	15	10301	22711
Russian controls	.	RS130628	11	15378	5731
Russian controls	.	RS130646	34	6464	8199
Russian controls	.	RS130657	12	27255	52183
Russian controls	.	RS130683	27	5308	8836
Russian controls	.	RS130684	16	5443	15775
Russian controls	.	RS130754	49	6631	18856
Russian controls	.	RS130755	21	6563	7160
Russian controls	.	RS130838	15	6551	9819
Russian controls	.	RS130858	17	12311	13522
Russian controls	.	RS130916	18	7035	6760
Russian controls	.	RS130923	25	36066	27208
Russian controls	.	RS130924	47	19136	22052
Russian controls	.	RS130940	12	27769	10186
Russian controls	.	RS130987	49	14286	19799
Russian controls	.	RS130990	18	6603	5783
Russian controls	.	RS131000	57	7318	14363
Russian controls	.	RS131008	32	17173	23436
Russian controls	.	RS131034	33	13411	21598
Russian controls	.	RS131052	53	8762	11738
Russian controls	.	RS131053	54	5655	8722
Russian controls	.	RS131054	14	17656	6417
Russian controls	.	RS131066	18	10839	12914
Russian controls	.	RS131093	27	30050	106773
Russian controls	.	RS131102	24	10452	6114
Russian controls	.	RS131160	19	16287	7922
Russian controls	.	RS131171	18	28416	32141
Russian controls	.	RS131225	18	14293	10735
Russian controls	.	RS131227	17	5607	9177
Russian controls	.	RS131246	25	8674	6374
Russian controls	.	RS131255	47	26441	12545
Russian controls	.	RS131271	25	23177	29339
Russian controls	.	RS131286	20	20060	25456
Russian controls	.	RS131333	28	7321	7781
Russian controls	.	RS131358	16	8790	21384
Russian controls	.	RS131359	13	24321	28569
Russian controls	.	RS131378	18	22119	26472
Russian controls	.	RS131395	16	8445	16983
Russian controls	.	RS131396	12	11020	36075
Russian controls	.	RS131413	60	7946	15100
Russian controls	.	RS131427	21	8930	7164
Russian controls	.	RS131464	18	6377	9596
Russian controls	.	RS131494	29	6386	6245
Russian controls	.	RS131496	21	5327	5482
Russian controls	.	RS131509	19	8539	9069
Russian controls	.	RS131549	27	6948	35636
Russian controls	.	RS131557	16	5994	8849
Russian controls	.	RS131568	17	6228	5329
Russian controls	.	RS131572	29	5785	10473
Russian controls	.	RS131578	29	6481	16336
Russian controls	.	RS131600	27	34208	16946
Russian controls	.	RS131619	72	6222	7206
Russian controls	.	RS131645	27	8271	5977
Russian controls	.	RS131662	13	24085	9346
Russian controls	.	RS131679	15	20496	10800
Russian controls	.	RS131703	13	22727	6189
Russian controls	.	RS131851	23	9837	17895
Russian controls	.	RS132024	37	15575	20967
Russian controls	.	RS132146	13	19589	21190
Russian controls	.	RS132156	15	9655	5470
Russian controls	.	RS132166	23	12381	7429
Russian controls	.	RS132168	115	30264	25450
Russian controls	.	RS132237	19	9290	27562
Russian controls	.	RS132271	15	9890	9123
Russian controls	.	RS132295	15	7562	21610
Russian controls	.	RS132305	19	17298	18449
Russian controls	.	RS132347	17	5630	6067
Russian controls	.	RS132352	19	6909	9414
Russian controls	.	RS132353	57	5652	6467
Russian controls	.	RS132363	16	7839	10628
Russian controls	.	RS132369	13	5298	16213
Russian controls	.	RS132393	30	5133	10689
Russian controls	.	RS132430	30	8981	5395
Russian controls	.	RS132666	106	9326	10146
Russian controls	.	RS132730	13	20139	10898
Russian controls	.	RS132751	14	15817	5426
Russian controls	.	RS132774	20	14220	6117
Russian controls	.	RS132837	55	6325	5265
Russian controls	.	RS133087	34	5974	36209
Russian controls	.	RS133347	28	14426	7839
Russian controls	.	RS133365	13	12716	35414
Russian controls	.	RS133494	15	12308	7815
Russian controls	.	RS133522	21	6201	16800

Table S3. Overview of the *TP53* mutations found in the plasma of 51 Russian SCLC patients with the mutations' allelic fractions (AF, %) detected in the two libraries, in both cfDNA and white-blood cells if applicable (NA, not done). *TP53* mutations are mapped to GenBank reference sequence NM_000546.

		Detected in cfDNA			Detected in white-blood cells	
Sample	**Tumour stage**	***TP53* mutation**	**Smallest AF**	**Highest AF**	**Smallest AF**	**Highest AF**
SCLC-1	IB	p.E204*	1.95	4.22		
SCLC-2	IIB	p.R156P	0.67	0.82		
SCLC-3	IIB	P.G154V	0.61	1.13	NA	NA
SCLC-4	IIIA	P.K164E	5.86	7.33		
SCLC-5	IB	p.V272M	0.40	0.54		
SCLC-6	IIB	p.V216M	1.02	1.11		
		e7-2	0.76	1.46		
SCLC-7	IIIA	p.P177R	0.26	0.42	NA	NA
		p.Q104*	6.88	11.49		
SCLC-8	IIIA	p.G245fs	0.42	0.71		
		p.G245V	7.91	13.82		
SCLC-9	IIIA	p.G244C	6.36	8.69		
SCLC-10	IIIA	p.E286*	57.6	60.52	NA	NA
SCLC-11	IIIA	p.V157F	25.04	28.05		
		p.V153fs	57.31	84.08		
SCLC-12	IV	p.L194R	0.12	0.19		
SCLC-13	IIIB	p.H179R	23.89	24.25		
SCLC-14	IV	p.S241fs	0.39	0.57		
		p.S241Y	77.47	84.81		
SCLC-15	IIIA	p.G245V	2.38	2.96		
SCLC-16	IIIA	p.R280*	34.72	37.23	NA	NA
SCLC-17	IV	p.C176Y	6.07	9.64		
SCLC-18	IIIA	p.H179R	1.57	3.20	NA	NA
SCLC-19	IV	p.P72fs	23.94	24.27		
SCLC-20	IIIB	p.P34fs	4.56	4.69		
SCLC-21	IIIB	p.R280G	11.41	11.65		
		p.Y220C	0.90	1.27	0.50	0.70
SCLC-22	IIIB	p.E271V	0.71	0.88		
SCLC-23	IIIB	p.Y163C	0.26	0.27		
SCLC-24	IIIA	p.G244V	15.37	16.86		
SCLC-25	IV	e7-1	61.20	67.18	NA	NA

Table S4. Overview of the *TP53* mutations found in the plasma of 123 non-cancer Russian controls with the mutations' allelic fractions (AF, %) detected in the two libraries, in both cfDNA and white-blood cells if applicable (NA, not done). TA refers to the mutations' functional classification based on the overall transcriptional activity from the IARC *TP53* database. *TP53* mutations are mapped to GenBank reference sequence NM_000546.

	Detected in cfDNA				Detected in white-blood cells		
Sample	***TP53* mutation**	**TA**	**Smallest AF**	**Highest AF**	**Smallest AF**	**Highest AF**	**Comments**
MLT-1	p.K291E	F	0.65	0.96			
MLT-2	p.E258fs		0.23	0.38			
MLT-3	p.H214Y	PF	0.27	4.04	NA	NA	
MLT-4	p.C275W	NF	0.24	0.61			
MLT-5	p.P34L	NF	1.14	1.19			
	p.E346A	F	0.26	0.85			
	p.C238Y	NF	0.50	0.61			
MLT-6	p.R175G	NF	4.09	4.41	4.40	4.50	
	p.R175H	NF	1.31	2.05			
	p.S261T	ST	1.01	1.50			
MLT-7	p.D281E	NF	79.85	84.94			
MLT-8	p.Y205*		0.19	0.49	NA	NA	
MLT-9	p.R273H	NF	1.05	2.50	NA	NA	
MLT-10	p.K382fs		13.68	14.46			
MLT-11	p.R175H	NF	20.92	21.28			
MLT-12	p.G244C	NF	0.33	0.74	NA	NA	
MLT-13	p.144-145del		3.02	5.32			
MLT-14	p.G154S	PF	47.17	50.58	52.10	54.90	likely germline

NF: non-functional

F: functional

PF: partially functional

ST: supertrans

Table S5. Overview of the *TP53* mutations found in the plasma of 9 Greece, 14 Czech Republic (CRE), 40 Italy (ITA), and 39 Argentina (ARG) non-cancer controls with the mutations' allelic fractions (AF, %) detected in the two libraries, in both cfDNA and white-blood cells if applicable (NA, not done). TA refers to the mutations' functional classification based on the overall transcriptional activity from the IARC *TP53* database. *TP53* mutations are mapped to GenBank reference sequence NM_000546.

	Detected in cfDNA				Detected in white-blood cells		
Sample	***TP53* mutation**	**TA**	**Smallest AF**	**Highest AF**	**Smallest AF**	**Highest AF**	**Comments**
ARG-1	p.R273C	NF	5.22	5.58	7.30	10.40	
ARG-2	p.G105S	NF	0.78	1.99			
ARG-3	p.K139R	F	0.47	0.88			
	p.E271V	NF	0.51	0.60			
ARG-4	p.F341C	NF	0.33	0.47			
CRE-5	p.F212fs		0.02	0.05			
	p.S269N	PF	0.18	0.82			
CRE-6	p.I254N	NF	0.07	0.09			
ITA-7	p.S241C	NF	0.06	0.10			
ITA-8	p.V272M	NF	0.78	0.80	0.90	1.40	
ITA-9	p.G302W	F	0.28	0.42			
ITA-10	p.R273L	NF	0.14	0.19			
ITA-11	p.T377I	F	55.84	63.74	NA	NA	likely germline

NF: non-functional

F: functional

PF: partially functional