

Susceptibility gene mutations in germline and tumors of patients with HER2-negative advanced breast cancer

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Supplementary Methods

Clinical Data collection

Data were collected and documented in electronic case report forms by trained staff [1] and monitored using automated plausibility checks and on-site monitoring. Epidemiological data such as family history, cancer risk factors, quality of life, nutrition and lifestyle items and psychological health that are not usually documented as part of routine clinical work, were collected prospectively using structured paper questionnaires (Supplementary Table S10).

Definition of hormone receptor, HER2 status, and grading

Definition of tumor hormone receptor status, HER2 status and grade was described before [2]. Briefly, estrogen receptor (ER) status, progesterone receptor (PR) status, HER2 status and grade were requested for biopsies from the right breast, left breast, local recurrence, or metastatic site of each tumor. If a biomarker assessment of the metastatic site was available, the receptor status was used for this analysis. In case of missing information from metastases, the latest biomarker results from the primary tumor were used. Additionally, all patients ever treated with prior endocrine therapy were assumed to be hormone receptor positive and all patients ever treated with an anti-HER2 therapy were assumed to be HER2 positive. There was no central review of biomarkers. ER and PR were considered positive if $\geq 1\%$ of tumor cells were stained. A positive HER2 status required an IHC score of 3+ or a positive FISH/CISH.

Supplementary references

1. Fasching PA, Brucker SY, Fehm TN et al. Biomarkers in Patients with Metastatic Breast Cancer and the PRAEGNANT Study Network. *Geburtshilfe Frauenheilkd* 2015; 75: 41-50.
2. Hartkopf AD, Huober J, Volz B et al. Treatment landscape of advanced breast cancer patients with hormone receptor positive HER2 negative tumors - Data from the German PRAEGNANT breast cancer registry. *Breast* 2018; 37: 42-51.

Supplementary Tables

Supplementary Table 1: Therapy line in which chemotherapy was started, according to hormone receptor status. Data is presented as *N* (%)

Therapy line	Hormone receptor status	
	Positive (<i>N</i> =388)	Negative (<i>N</i> =76)
1	172 (44.3)	68 (89.5)
2	80 (20.6)	7 (9.2)
3	83 (21.4)	1 (1.3)
4+	53 (13.7)	0 (0.0)

Supplementary Table 2: Breast Cancer Risk Factors in correlation to germline genotyping results. Data is presented as *N* (%) [BC: breast cancer; TNBC: triple-negative breast cancer]

Characteristics		No mutation (<i>N</i> =415)	gBRCAm (<i>N</i> =23)	Other BC Risk Genes (<i>N</i> =33)
Diagnosis before age 46	No	298 (71.8)	12 (52.2)	24 (72.7)
	Yes	117 (28.2)	11 (47.8)	9 (27.3)
	Missing values	0 (0.0)	0 (0.0)	0 (0.0)
Bilateral BC before age 51	No	402 (96.9)	17 (73.9)	31 (93.9)
	Yes	13 (3.1)	6 (26.1)	2 (6.1)
	Missing values	0 (0.0)	0 (0.0)	0 (0.0)
Diagnosis before age 51 and one further 1st line relative with BC	No	393 (94.7)	18 (78.3)	30 (90.9)
	Yes	22 (5.3)	5 (21.7)	3 (9.1)
	Missing values	0 (0.0)	0 (0.0)	0 (0.0)
Diagnosis before age 61 and TNBC	No	372 (89.6)	17 (73.9)	30 (90.9)
	Yes	43 (10.4)	6 (26.1)	3 (9.1)
	Missing values	0 (0.0)	0 (0.0)	0 (0.0)
Diagnosis after age 50 and one 1st line relative with BC under age 51	No	412 (99.3)	22 (95.7)	33 (100.0)
	Yes	3 (0.7)	1 (4.3)	0 (0.0)
	Missing values	0 (0.0)	0 (0.0)	0 (0.0)
More than 2 BC cases in this family	No	409 (98.6)	22 (95.7)	31 (93.9)
	Yes	6 (1.4)	1 (4.3)	2 (6.1)
	Missing values	0 (0.0)	0 (0.0)	0 (0.0)
1st line relative with ovarian cancer	No	404 (97.3)	21 (91.3)	32 (97.0)
	Yes	11 (2.7)	2 (8.7)	1 (3.0)
	Missing values	0 (0.0)	0 (0.0)	0 (0.0)
Male relative with BC	No	405 (97.6)	22 (95.7)	32 (97.0)
	Yes	10 (2.4)	1 (4.3)	1 (3.0)
	Missing values	0 (0.0)	0 (0.0)	0 (0.0)
Own history of ovarian cancer	No	414 (99.8)	22 (95.7)	32 (97.0)
	Yes	1 (0.2)	1 (4.3)	1 (3.0)
	Missing values	0 (0.0)	0 (0.0)	0 (0.0)
Any reason for genotyping	No	250 (60.2)	6 (26.1)	18 (54.5)
	Yes	165 (39.8)	17 (73.9)	15 (45.5)
	Missing values	0 (0.0)	0 (0.0)	0 (0.0)

Supplementary Table 3: List of all mutations and their frequency from the germline genotyping (table on mutation level, not gene level, not patient level) (*N*=471)

Gene Name	HGVS mutation nomenclature	Mutation count in the total population of 471 patients
<i>APC</i>	c.5565T>A_p.Cys1855X	1
<i>ATM</i>	c.3802delG	1
<i>BARD1</i>	c.1872delT	1
<i>BLM</i>	c.1933C>T_p.Gln645X	1
<i>BLM</i>	c.2695C>T_p.Arg899X	1
<i>BRCA1</i>	c.1687C>T_p.Gln563X	1
<i>BRCA1</i>	c.181T>G_p.Cys61Gly	1
<i>BRCA1</i>	c.3481_3491del11	1
<i>BRCA1</i>	c.4065_4068delTCAA	1
<i>BRCA1</i>	c.4932_4933dupAA	1
<i>BRCA1</i>	c.4986+3G>C	1
<i>BRCA1</i>	c.5109T>G_p.Tyr1703X	1
<i>BRCA1</i>	c.5266dupC	3
<i>BRCA2</i>	c.1296_1297delGA	1
<i>BRCA2</i>	c.1813dupA	1
<i>BRCA2</i>	c.2808_2811delACAA	2
<i>BRCA2</i>	c.516+2T>A	1
<i>BRCA2</i>	c.5722_5723delCT	1
<i>BRCA2</i>	c.5857G>T_p.Glu1953X	1
<i>BRCA2</i>	c.7480C>T_p.Arg2494X	1
<i>BRCA2</i>	c.7816_7819dupGACA	1
<i>BRCA2</i>	c.7857G>A_p.Trp2619X	1
<i>BRCA2</i>	c.917dupA	1
<i>BRCA2</i>	c.9196C>T_p.Gln3066X	1
<i>BRIP1</i>	c.3241_3245dup5	1
<i>CDH1</i>	c.377dupC	1
<i>CHEK2</i>	c.1100delC	5
<i>CHEK2</i>	c.1375+1G>A	1
<i>CHEK2</i>	c.444+1G>A	1
<i>CHEK2</i>	exon 9-10 del	2
<i>ERCC2</i>	c.2150C>G_p.Ala717Gly	1
<i>FANCC</i>	c.37C>T_p.Gln13X	1
<i>FANCC</i>	c.455dupA	1
<i>FANCM</i>	c.3603delT	1
<i>FANCM</i>	exon 12-23 del	1
<i>MRE11A</i>	c.1516G>T_p.Glu506X	1
<i>MRE11A</i>	c.1726C>T_p.Arg576X	1
<i>MSH6</i>	c.3226C>T_p.Arg1076Cys	1
<i>MSH6</i>	c.3991C>T_p.Arg1331X	1
<i>MUTYH</i>	c.1171C>T_p.Gln391X	1
<i>PALB2</i>	c.1424dupC	1
<i>PALB2</i>	c.1451T>A_p.Leu484X	1
<i>PALB2</i>	c.2257C>T_p.Arg753X	1
<i>PALB2</i>	c.3456dupA	1

Gene Name	HGVS mutation nomenclature	Mutation count in the total population of 471 patients
<i>PALB2</i>	c.3549C>A_p.Tyr1183X	1
<i>PALB2</i>	c.487_488delGT	1
<i>PALB2</i>	c.509_510delGA	1
<i>PMS2</i>	c.1882C>T_p.Arg628X	1
<i>PPM1D</i>	c.1303dupC	1
<i>PPM1D</i>	c.1451delT	1
<i>PRSS1</i>	c.256C>T_p.Gln86X	1
<i>PRSS1</i>	exon 1-4 del	1
<i>PRSS1</i>	exon 2-5 del	1
<i>PTEN</i>	c.875dupA	1
<i>RAD50</i>	c.3454C>T_p.Arg1152X	1
<i>RAD50</i>	exon 4-14 del	1
<i>RAD51C</i>	c.414G>C_p.Leu138Phe	1
<i>RAD51C</i>	c.706-2A>G	1
<i>RAD51D</i>	c.694C>T_p.Arg232X	1
<i>RECQL</i>	c.1099-2A>C	1
<i>RECQL</i>	c.1476C>G_p.Tyr492X	1
<i>RINT1</i>	c.1333+1G>A	1
<i>TP53</i>	c.734G>T_p.Gly245Val	1
<i>XRCC2</i>	c.96delT	1

Supplementary Table 4: Patient Characteristics according to somatic mutation status
(N=94)

Characteristics		No mutation (N=33)	sBRCAm (N=2)	Other BC Risk Genes (N=59)
Age at study entry (years)	N with value	33	2	59
	Mean (SD)	61.1 (13.2)	65.5 (10.6)	55.8 (14.0)
	Median (IQR)	64 (50, 72)	65.5 (61.8, 69.2)	56 (46, 66.5)
	Range (min, max)	(35, 82)	(58, 73)	(29, 81)
	Missing values	0	0	0
BMI (kg/m ²)	N with value	30	2	51
	Mean (SD)	25.3 (5.5)	28.2 (0.5)	26.9 (4.7)
	Median (IQR)	25.2 (20.7, 27.8)	28.2 (28.1, 28.4)	26.3 (24.1, 29.9)
	Range (min, max)	(18.4, 41.1)	(27.9, 28.6)	(16.3, 38.9)
	<18.5	1 (3.0)	0 (0.0)	2 (3.4)
	18.5 - <25	13 (39.4)	0 (0.0)	15 (25.4)
	25 - <30	10 (30.3)	2 (100.0)	21 (35.6)
	≥30	6 (18.2)	0 (0.0)	13 (22.0)
	Missing values	3 (9.1)	0 (0.0)	8 (13.6)
Hormone receptor status	HR-	3 (9.1)	0 (0.0)	12 (20.3)
	HR+	30 (90.9)	2 (100.0)	47 (79.7)
	Missing values	0 (0.0)	0 (0.0)	0 (0.0)
Tumor grade	1	0 (0.0)	0 (0.0)	2 (3.4)
	2	21 (63.6)	2 (100.0)	21 (35.6)
	3	10 (30.3)	0 (0.0)	35 (59.3)
	Missing values	2 (6.1)	0 (0.0)	1 (1.7)
Therapy line	1	13 (39.4)	1 (50.0)	34 (57.6)
	2	9 (27.3)	1 (50.0)	15 (25.4)
	3	3 (9.1)	0 (0.0)	7 (11.9)
	4+	8 (24.2)	0 (0.0)	3 (5.1)
	Missing values	0 (0.0)	0 (0.0)	0 (0.0)
ECOG performance status	0	16 (48.5)	2 (100.0)	30 (50.8)
	1	13 (39.4)	0 (0.0)	18 (30.5)
	2+	3 (9.1)	0 (0.0)	7 (11.9)
	Missing values	1 (3.0)	0 (0.0)	4 (6.8)
Metastasis pattern	Brain	1 (3.0)	0 (0.0)	7 (11.9)
	Visceral	21 (63.6)	2 (100.0)	27 (45.8)
	Bone	6 (18.2)	0 (0.0)	7 (11.9)
	Others	5 (15.2)	0 (0.0)	17 (28.8)
	Missing values	0 (0.0)	0 (0.0)	1 (1.7)
Concomitant diseases	0 or 1	16 (48.5)	2 (100.0)	30 (50.8)
	2 to 4	13 (39.4)	0 (0.0)	18 (30.5)
	5+	3 (9.1)	0 (0.0)	8 (13.6)
	Missing values	1 (3.0)	0 (0.0)	3 (5.1)

Supplementary Table 5: Cumulative results of the Foundation Medicine FoundationOne Dx Panel analysis of the somatic genotyping population - Frequencies of patients with a found short variant (SV), copy number alteration (CNA) and rearrangement (REARR)

Gene	Frequency of SV (N=94) - N (%)	Frequency of CNA (N=94) - N (%)	Frequency of REARR (N=94) - N (%)
<i>AKT1</i>	3 (3.2)	1 (1.1)	
<i>AKT3</i>		2 (2.1)	
<i>APC</i>			2 (2.1)
<i>AR</i>		1 (1.1)	
<i>ARAF</i>	1 (1.1)		
<i>ARFRP1</i>		4 (4.3)	
<i>ARID1A</i>	9 (9.6)		
<i>ASXL1</i>	1 (1.1)		1 (1.1)
<i>ATM</i>	4 (4.3)		1 (1.1)
<i>ATR</i>	1 (1.1)		
<i>ATRX</i>	1 (1.1)		
<i>AURKA</i>		3 (3.2)	
<i>AURKB</i>		1 (1.1)	
<i>BCL2L1</i>		2 (2.1)	
<i>BCOR</i>	1 (1.1)		
<i>BRAF</i>			2 (2.1)
<i>BRCA2</i>	2 (2.1)		
<i>BRD4</i>	1 (1.1)		1 (1.1)
<i>BRIP1</i>			2 (2.1)
<i>BTG2</i>			1 (1.1)
<i>CASP8</i>	1 (1.1)		
<i>CBFB</i>	2 (2.1)		
<i>CCND1</i>		23 (24.5)	
<i>CCND2</i>		1 (1.1)	
<i>CCND3</i>		1 (1.1)	
<i>CCNE1</i>		3 (3.2)	
<i>CD274</i>		1 (1.1)	1 (1.1)
<i>CDH1</i>	10 (10.6)		1 (1.1)
<i>CDK6</i>		1 (1.1)	
<i>CDK8</i>		1 (1.1)	
<i>CDKN1B</i>	1 (1.1)		
<i>CDKN2A</i>	1 (1.1)	8 (8.5)	
<i>CDKN2B</i>		6 (6.4)	
<i>CHEK1</i>	1 (1.1)		
<i>CHEK2</i>	4 (4.3)		1 (1.1)
<i>CREBBP</i>	2 (2.1)		
<i>CSF3R</i>		1 (1.1)	
<i>CTNNA1</i>	1 (1.1)	1 (1.1)	
<i>CTNNB1</i>	1 (1.1)		
<i>CUL4A</i>		1 (1.1)	
<i>EMSY</i>		10 (10.6)	
<i>EPHB4</i>		1 (1.1)	
<i>ERBB2</i>	3 (3.2)	4 (4.3)	

Gene	Frequency of SV (N=94) - N (%)	Frequency of CNA (N=94) - N (%)	Frequency of REARR (N=94) - N (%)
<i>ERBB3</i>	2 (2.1)		1 (1.1)
<i>ERBB4</i>	1 (1.1)		
<i>ERCC4</i>	1 (1.1)		
<i>ESR1</i>	9 (9.6)	1 (1.1)	
<i>EZH2</i>	1 (1.1)		1 (1.1)
<i>FAM123B</i>			1 (1.1)
<i>FAS</i>		1 (1.1)	
<i>FGF12</i>		1 (1.1)	
<i>FGF19</i>		22 (23.4)	
<i>FGF23</i>		2 (2.1)	
<i>FGF3</i>		21 (22.3)	
<i>FGF4</i>		21 (22.3)	
<i>FGF6</i>		2 (2.1)	
<i>FGFR1</i>		16 (17)	2 (2.1)
<i>FGFR2</i>	1 (1.1)		
<i>FGFR4</i>		2 (2.1)	
<i>FUBP1</i>			1 (1.1)
<i>GABRA6</i>	1 (1.1)		
<i>GATA3</i>	16 (17)		
<i>GNAS</i>		4 (4.3)	1 (1.1)
<i>GRM3</i>	1 (1.1)		
<i>HGF</i>		2 (2.1)	
<i>HRAS</i>		1 (1.1)	
<i>IGF1R</i>		1 (1.1)	
<i>IKBKE</i>		2 (2.1)	
<i>IRS2</i>		2 (2.1)	
<i>JAK2</i>		1 (1.1)	1 (1.1)
<i>JUN</i>		1 (1.1)	
<i>KDM5A</i>		4 (4.3)	
<i>KDM5C</i>	1 (1.1)		1 (1.1)
<i>KDR</i>	1 (1.1)		
<i>KEL</i>	1 (1.1)		
<i>KLHL6</i>	1 (1.1)		
<i>KRAS</i>	2 (2.1)	2 (2.1)	
<i>LYN</i>		6 (6.4)	
<i>MAP2K1</i>	1 (1.1)	1 (1.1)	
<i>MAP2K4</i>	3 (3.2)	7 (7.4)	
<i>MAP3K1</i>	7 (7.4)		
<i>MCL1</i>		4 (4.3)	
<i>MDM2</i>		4 (4.3)	
<i>MDM4</i>		5 (5.3)	
<i>MEN1</i>	3 (3.2)		
<i>MRE11A</i>	1 (1.1)		
<i>MSH3</i>	1 (1.1)		
<i>MTAP</i>		8 (8.5)	
<i>MUTYH</i>	1 (1.1)		
<i>MYB</i>			1 (1.1)

Gene	Frequency of SV (N=94) - N (%)	Frequency of CNA (N=94) - N (%)	Frequency of REARR (N=94) - N (%)
MYC		18 (19.1)	
MYCL1		1 (1.1)	
NBN			1 (1.1)
NF1	6 (6.4)	1 (1.1)	2 (2.1)
NFE2L2	1 (1.1)		
NFKBIA		1 (1.1)	1 (1.1)
NOTCH1	3 (3.2)		
NOTCH2	1 (1.1)		2 (2.1)
NOTCH3		1 (1.1)	
PALB2	1 (1.1)		
PARP1		1 (1.1)	
PDCD1LG2		1 (1.1)	
PIK3C2B		7 (7.4)	1 (1.1)
PIK3CA	30 (31.9)	2 (2.1)	
PIK3R1	5 (5.3)		
POLD1			1 (1.1)
POLE			1 (1.1)
PPP2R1A	1 (1.1)		
PRKCI		1 (1.1)	
PTEN	6 (6.4)	5 (5.3)	2 (2.1)
RAD21		23 (24.5)	
RAD51D	1 (1.1)		
RAF1		1 (1.1)	
RB1	1 (1.1)	1 (1.1)	1 (1.1)
REL	1 (1.1)		
RET	1 (1.1)		
RICTOR		2 (2.1)	
RNF43	1 (1.1)		
ROS1		1 (1.1)	
SDHB	1 (1.1)		
SMAD4	1 (1.1)		
SMARCA4			1 (1.1)
SMARCB1	1 (1.1)		
SOX9	1 (1.1)		
SPEN	7 (7.4)		
SPOP	1 (1.1)		
STK11	1 (1.1)	1 (1.1)	
SUFU		()	1 (1.1)
TBX3	5 (5.3)	1 (1.1)	
TERC		2 (2.1)	
TET2	1 (1.1)		
TNFAIP3	2 (2.1)		
TNFRSF14			1 (1.1)
TP53	42 (44.7)	1 (1.1)	1 (1.1)
VEGFA		2 (2.1)	
VHL	1 (1.1)		
WHSC1L1		17 (18.1)	2 (2.1)

Gene	Frequency of SV (<i>N</i> =94) - <i>N</i> (%)	Frequency of CNA (<i>N</i> =94) - <i>N</i> (%)	Frequency of REARR (<i>N</i> =94) - <i>N</i> (%)
<i>ZNF217</i>		5 (5.3)	1 (1.1)
<i>ZNF703</i>		16 (17)	

Supplementary Table 6: Listing of all mutations and their frequency from the somatic genotyping (list on mutation level, not gene level, not patient level) in *N*=94 patients

Gene	HGVS mutation nomenclature	<i>N</i>
<i>AKT1</i>	c.226_227insAGACGGAGCGGCCCGGCCCAACACCTTCATCATCC; p.I75_R76insQTERPRPNTFII	1
<i>AKT1</i>	c.239_240insCACGGAGCGGCCCGGCCCAACACCTTCATCATCCGCTGCC TGCAGTG; p.Q79_W80insCTERPRPNTFIIRCLQ	1
<i>AKT1</i>	c.49G>A; p.E17K	1
<i>ARAF</i>	c.1702G>C; p.E568Q	1
<i>ARID1A</i>	c.1543C>T; p.Q515*	1
<i>ARID1A</i>	c.2147delC; p.P716fs*26	1
<i>ARID1A</i>	c.3175_3176insGAAACCTCTGGACCTCTATCGCCTCTATGTGTCTGTGA; p.K1059fs*13	1
<i>ARID1A</i>	c.3634C>T; p.Q1212*	1
<i>ARID1A</i>	c.4189C>T; p.Q1397*	1
<i>ARID1A</i>	c.5975C>G; p.S1992*	1
<i>ARID1A</i>	c.6291_6378del88; p.E2098fs*8	1
<i>ARID1A</i>	c.6415_6416insT; p.P2139fs*11	1
<i>ARID1A</i>	c.6749_6750delAG; p.E2250fs*27	1
<i>ASXL1</i>	c.4019_4026delCAAGCACA; p.P1340fs*28	1
<i>ATM</i>	c.1010G>A; p.R337H	1
<i>ATM</i>	c.3799G>T; p.E1267*	1
<i>ATM</i>	c.7015_7016delAG; p.R2339fs*33	1
<i>ATM</i>	c.8158G>C; p.D2720H	1
<i>ATR</i>	c.4153-258_4204del310; p.splice site 4153-258_4204del310	1
<i>ATRX</i>	c.3580A>T; p.K1194*	1
<i>BCOR</i>	c.3622C>T; p.Q1208*	1
<i>BRCA2</i>	c.1898delA; p.N633fs*11	1
<i>BRCA2</i>	c.9155G>A; p.R3052Q	1
<i>BRD4</i>	c.4021-1G>C; p.splice site 4021-1G>C	1
<i>CASP8</i>	c.1279_1280delGT; p.V427fs*28	1
<i>CBFB</i>	c.78+1G>A; p.splice site 78+1G>A	1
<i>CBFB</i>	c.97_110delAGGGACCGGCCCA; p.D34fs*44	1
<i>CDH1</i>	c.1792C>T; p.R598*	1
<i>CDH1</i>	c.1921C>T; p.Q641*	1
<i>CDH1</i>	c.1955delT; p.L652fs*1	1
<i>CDH1</i>	c.1993delA; p.I665fs*14	1
<i>CDH1</i>	c.220C>T; p.R74*	1
<i>CDH1</i>	c.2460_2463delTGAC; p.D821fs*24	1
<i>CDH1</i>	c.67C>T; p.Q23*	2
<i>CDH1</i>	c.81delC; p.C28fs*28	1
<i>CDH1</i>	c.832+1G>T; p.splice site 832+1G>T	1
<i>CDKN1B</i>	c.340_347delCCGGCGGC; p.P114fs*8	1
<i>CDKN2A</i>	c.151-1G>A; p.splice site 151-1G>A	1
<i>CHEK1</i>	c.515C>A; p.P172Q	1
<i>CHEK2</i>	c.1100delC; p.T367fs*15	1
<i>CHEK2</i>	c.470T>C; p.I157T	3
<i>CREBBP</i>	c.4328_4332delGTTGC; p.R1443fs*8	1
<i>CREBBP</i>	c.86-1G>C; p.splice site 86-1G>C	1
<i>CTNNA1</i>	c.966_967insAAGCATCATTAGTGGGGCTGCCTTGATGGCCGACTCG; p.S323fs*4	1

Gene	HGVS mutation nomenclature	N
<i>CTNNB1</i>	c.1400_1413delCTCTTCGTCATCTG; p.A467fs*25	1
<i>ERBB2</i>	c.2089G>C; p.V697L	1
<i>ERBB2</i>	c.2264T>C; p.L755S	2
<i>ERBB2</i>	c.2325_2326insTACGTGATGGCT; p.A775_G776insYVMA	1
<i>ERBB3</i>	c.2783A>G; p.E928G	1
<i>ERBB3</i>	c.850G>C; p.G284R	1
<i>ERBB4</i>	c.908C>T; p.S303F	1
<i>ERCC4</i>	c.2395C>T; p.R799W	1
<i>ESR1</i>	c.1138G>C; p.E380Q	2
<i>ESR1</i>	c.1609T>A; p.Y537N	2
<i>ESR1</i>	c.1610A>C; p.Y537S	1
<i>ESR1</i>	c.1610A>G; p.Y537C	1
<i>ESR1</i>	c.1613A>G; p.D538G	3
<i>EZH2</i>	c.435C>G; p.F145L	1
<i>FGFR2</i>	c.1647T>A; p.N549K	1
<i>GABRA6</i>	c.682G>A; p.V228I	1
<i>GATA3</i>	c.1006_1007insG; p.D336fs*17	1
<i>GATA3</i>	c.1051-46_1164del160; p.splice site 1051-46_1164del160	1
<i>GATA3</i>	c.1089_1122del34; p.T364fs*30	1
<i>GATA3</i>	c.1211_1212insC; p.S405fs*103	1
<i>GATA3</i>	c.1223_1224insC; p.P409fs*99	1
<i>GATA3</i>	c.1224_1225insG; p.P409fs*99	2
<i>GATA3</i>	c.1239_1240insC; p.S414fs*94	1
<i>GATA3</i>	c.1263_1264insG; p.P422fs*86	1
<i>GATA3</i>	c.1266_1270delGATGC; p.M423fs*83	1
<i>GATA3</i>	c.1277_1278insCCGCC; p.S427fs*51	1
<i>GATA3</i>	c.1287_1288delGT; p.S430fs*77	1
<i>GATA3</i>	c.1315delA; p.M439fs*37	1
<i>GATA3</i>	c.881T>A; p.M294K	1
<i>GATA3</i>	c.988_989delAG; p.R330fs*22	1
<i>GATA3</i>	c.988_989insA; p.R330fs*23	1
<i>GRM3</i>	c.2273C>T; p.T758M	1
<i>KDM5C</i>	c.2293_2510del344; p.splice site 2293_2510del344	1
<i>KDR</i>	c.1860C>A; p.S620R	1
<i>KEL</i>	c.2T>C; p.M1T	1
<i>KLHL6</i>	c.821C>T; p.T274M	1
<i>KRAS</i>	c.34G>T; p.G12C	1
<i>KRAS</i>	c.35G>T; p.G12V	1
<i>MAP2K1</i>	c.607G>A; p.E203K	1
<i>MAP2K4</i>	c.1086+1G>A; p.splice site 1086+1G>A	1
<i>MAP2K4</i>	c.328C>T; p.R110*	1
<i>MAP2K4</i>	c.921T>A; p.Y307*	1
<i>MAP3K1</i>	c.1013_1014insA; p.Y338fs*1	1
<i>MAP3K1</i>	c.1331_1332insC; p.I445fs*8	1
<i>MAP3K1</i>	c.1486delA; p.R496fs*61	1
<i>MAP3K1</i>	c.2187delT; p.I729fs*10	1
<i>MAP3K1</i>	c.2242_2245delTCAA; p.S748fs*13	1
<i>MAP3K1</i>	c.3879_3883delAGAGA; p.E1293fs*14	1
<i>MAP3K1</i>	c.4050_4051insACACT; p.E1351fs*28	1
<i>MAP3K1</i>	c.4144C>T; p.Q1382*	1

Gene	HGVS mutation nomenclature	N
MAP3K1	c.4390-1G>C; p.splice site 4390-1G>C	1
MAP3K1	c.862C>T; p.R288*	1
MEN1	c.166_187del22; p.T56fs*56	1
MEN1	c.505delG; p.A169fs*21	1
MEN1	c.898_902delCGGCC; p.D302fs*18	1
MRE11A	c.1726C>T; p.R576*	1
MSH3	c.2436-1G>A; p.splice site 2436-1G>A	1
MUTYH	c.494A>G; p.Y165C	1
NF1	c.1660C>T; p.Q554*	1
NF1	c.4084C>T; p.R1362*	1
NF1	c.4195C>T; p.Q1399*	1
NF1	c.4543C>T; p.Q1515*	1
NF1	c.5902C>T; p.R1968*	1
NF1	c.6007-1G>A; p.splice site 6007-1G>A	1
NF1	c.7006G>A; p.A2336T	1
NF1	c.7591C>T; p.Q2531*	1
NFE2L2	c.242G>A; p.G81D	1
NOTCH1	c.4723G>C; p.V1575L	1
NOTCH1	c.7541_7542delCT; p.P2514fs*4	1
NOTCH1	c.7543G>T; p.E2515*	1
NOTCH2	c.3406C>T; p.Q1136*	1
PALB2	c.1424_1425insC; p.R476fs*11	1
PALB2	c.2257C>T; p.R753*	1
PIK3CA	c.1035T>A; p.N345K	3
PIK3CA	c.115G>A; p.E39K	1
PIK3CA	c.1252G>A; p.E418K	1
PIK3CA	c.1356_1382del27; p.L452_V461>F	1
PIK3CA	c.1357G>C; p.E453Q	1
PIK3CA	c.1624G>A; p.E542K	3
PIK3CA	c.1633G>A; p.E545K	8
PIK3CA	c.1634A>C; p.E545A	1
PIK3CA	c.311C>T; p.P104L	2
PIK3CA	c.3127A>G; p.M1043V	1
PIK3CA	c.3140A>G; p.H1047R	11
PIK3CA	c.3140A>T; p.H1047L	3
PIK3CA	c.3145G>C; p.G1049R	1
PIK3CA	c.320A>G; p.N107S	1
PIK3R1	c.1300-21_1304>G; p.splice site 1300-21_1304>G	1
PIK3R1	c.1323_1358del36; p.I442_N453del	1
PIK3R1	c.1325_1357del33; p.I442_Y452del	1
PIK3R1	c.1425+1G>A; p.splice site 1425+1G>A	1
PIK3R1	c.1724_1729delAGACGA; p.K575_T576del	1
PPP2R1A	c.767C>T; p.S256F	1
PTEN	c.203A>G; p.Y68C	1
PTEN	c.351_450del100; p.N117fs*3	1
PTEN	c.497_498insT; p.T167fs*13	1
PTEN	c.733C>T; p.Q245*	1
PTEN	c.763_770delGTAGAGTT; p.V255fs*40	1
PTEN	c.955_958delACTT; p.T319fs*1	1
RAD51D	c.694C>T; p.R232*	1

Gene	HGVS mutation nomenclature	N
<i>RB1</i>	c.2773_*34del49; p.K925fs*23	1
<i>REL</i>	c.1261C>T; p.R421C	1
<i>RET</i>	c.1799G>A; p.R600Q	1
<i>RNF43</i>	c.1820C>T; p.S607L	1
<i>SDHB</i>	c.151_152delAA; p.K51fs*11	1
<i>SMAD4</i>	c.1054G>A; p.G352R	1
<i>SMARCB1</i>	c.118C>T; p.R40*	1
<i>SOX9</i>	c.1079_1080insC; p.Q361fs*217	1
<i>SPEN</i>	c.10228_10229delAA; p.N3410fs*4	1
<i>SPEN</i>	c.10753C>T; p.Q3585*	1
<i>SPEN</i>	c.2227C>T; p.Q743*	1
<i>SPEN</i>	c.2761C>T; p.Q921*	1
<i>SPEN</i>	c.316_356del41; p.G106fs*11	1
<i>SPEN</i>	c.4111C>T; p.R1371*	1
<i>SPEN</i>	c.6932C>G; p.S2311*	1
<i>SPEN</i>	c.7499_7500delAG; p.E2500fs*26	1
<i>SPOP</i>	c.570A>C; p.L190F	1
<i>STK11</i>	c.592_597+5GCCGAGGTAGG>CCCCGA; p.splice site 592_597+5GCCGAGGTAGG>CCCCGA	1
<i>TBX3</i>	c.1416_1417delGC; p.L473fs*218	1
<i>TBX3</i>	c.1812delC; p.Y605fs*27	1
<i>TBX3</i>	c.1941_1942insTG; p.P648fs*242	1
<i>TBX3</i>	c.2144_2152AGCGGCCA>TT; p.E715fs*172	1
<i>TBX3</i>	c.628_632ACCAA>T; p.T210fs*32	1
<i>TBX3</i>	c.635_637delACA; p.N212del	1
<i>TET2</i>	c.5473C>T; p.Q1825*	1
<i>TNFAIP3</i>	c.1428G>A; p.M476I	1
<i>TNFAIP3</i>	c.499G>T; p.E167*	1
<i>TP53</i>	c.1014_1015delCG; p.F338fs*8	1
<i>TP53</i>	c.1015G>T; p.E339*	1
<i>TP53</i>	c.151G>T; p.E51*	1
<i>TP53</i>	c.227_279del53; p.A76fs*55	1
<i>TP53</i>	c.267delC; p.S90fs*33	1
<i>TP53</i>	c.329G>C; p.R110P	1
<i>TP53</i>	c.329G>T; p.R110L	1
<i>TP53</i>	c.358A>G; p.K120E	1
<i>TP53</i>	c.376-41_402del68; p.splice site 376-41_402del68	1
<i>TP53</i>	c.379T>A; p.S127T	1
<i>TP53</i>	c.399_400insG; p.F134fs*15	1
<i>TP53</i>	c.434T>C; p.L145P	2
<i>TP53</i>	c.445_466del22; p.S149fs*14	1
<i>TP53</i>	c.455_456insC; p.P153fs*28	1
<i>TP53</i>	c.488A>C; p.Y163S	1
<i>TP53</i>	c.524G>A; p.R175H	3
<i>TP53</i>	c.529_546delCCCCACCATGAGCGCTGC; p.P177_C182del	1
<i>TP53</i>	c.535_536insC; p.H179fs*2	1
<i>TP53</i>	c.536A>G; p.H179R	1
<i>TP53</i>	c.574C>T; p.Q192*	2
<i>TP53</i>	c.584T>C; p.I195T	1
<i>TP53</i>	c.586C>T; p.R196*	1

Gene	HGVS mutation nomenclature	N
<i>TP53</i>	c.594_602delAGGAAATTT; p.G199_L201del	1
<i>TP53</i>	c.637C>T; p.R213*	1
<i>TP53</i>	c.665C>T; p.P222L	1
<i>TP53</i>	c.672+1G>T; p.splice site 672+1G>T	1
<i>TP53</i>	c.700T>C; p.Y234H	1
<i>TP53</i>	c.722C>T; p.S241F	1
<i>TP53</i>	c.742C>G; p.R248G	1
<i>TP53</i>	c.743G>A; p.R248Q	1
<i>TP53</i>	c.814G>A; p.V272M	1
<i>TP53</i>	c.838A>G; p.R280G	1
<i>TP53</i>	c.839G>A; p.R280K	1
<i>TP53</i>	c.839G>C; p.R280T	1
<i>TP53</i>	c.844C>T; p.R282W	1
<i>TP53</i>	c.892G>T; p.E298*	1
<i>TP53</i>	c.916C>T; p.R306*	1
<i>TP53</i>	c.960G>C; p.K320N	1
<i>TP53</i>	c.993+2T>G; p.splice site 993+2T>G	1
<i>VHL</i>	c.5_6insGCGGAGGGAATGCC; p.A5fs*14	1

Supplementary Table 7: List of all copy-number-alterations (CNA) from the somatic genotyping (N=94)

Gene	Copy number	CNA exons	CNA ratio	CNA type	CNA position
<i>AKT1</i>	7	13 of 13	1.75	amplification	chr14:105187919-105302907
<i>AKT3</i>	7	14 of 14	2.08	amplification	chr1:243619000-244056522
<i>AKT3</i>	7	14 of 14	1.53	amplification	chr1:243627223-244056522
<i>AR</i>	10	9 of 9	3.03	amplification	chrX:66764988-66943683
<i>ARFRP1</i>	7	6 of 6	2.28	amplification	chr20:62282005-62383121
<i>ARFRP1</i>	7	6 of 6	2.13	amplification	chr20:62282005-62383121
<i>ARFRP1</i>	6	6 of 6	2.20	amplification	chr20:62282005-62383121
<i>ARFRP1</i>	12	6 of 6	5.13	amplification	chr20:62282005-62383121
<i>AURKA</i>	7	8 of 8	2.13	amplification	chr20:54897975-55013001
<i>AURKA</i>	6	8 of 8	2.57	amplification	chr20:54897975-55013001
<i>AURKA</i>	6	8 of 8	2.45	amplification	chr20:54897975-55013001
<i>AURKB</i>	11	8 of 8	3.63	amplification	chr17:8059789-8161279
<i>BCL2L1</i>	7	4 of 4	2.16	amplification	chr20:30253751-30310021
<i>BCL2L1</i>	8	4 of 4	2.00	amplification	chr20:30253751-30310021
<i>CCND1</i>	23	5 of 5	8.00	amplification	chr11:69412013-69502020
<i>CCND1</i>	9	5 of 5	1.92	amplification	chr11:69412013-69502020
<i>CCND1</i>	10	5 of 5	2.23	amplification	chr11:69412013-69502020
<i>CCND1</i>	7	5 of 5	3.12	amplification	chr11:69449390-69490355
<i>CCND1</i>	16	5 of 5	4.41	amplification	chr11:69412013-69502020
<i>CCND1</i>	68	5 of 5	15.14	amplification	chr11:69412013-69502020
<i>CCND1</i>	7	5 of 5	3.46	amplification	chr11:69412013-69502020
<i>CCND1</i>	7	5 of 5	2.14	amplification	chr11:69412013-69490355
<i>CCND1</i>	14	5 of 5	4.69	amplification	chr11:69412013-69502020
<i>CCND1</i>	16	5 of 5	2.75	amplification	chr11:69412013-69502020
<i>CCND1</i>	8	5 of 5	3.43	amplification	chr11:69412013-69502020
<i>CCND1</i>	9	5 of 5	2.46	amplification	chr11:69442323-69502020
<i>CCND1</i>	11	5 of 5	2.23	amplification	chr11:69412013-69502020
<i>CCND1</i>	8	5 of 5	3.66	amplification	chr11:69412013-69502020
<i>CCND1</i>	32	5 of 5	4.66	amplification	chr11:69412013-69502020
<i>CCND1</i>	23	5 of 5	6.82	amplification	chr11:69412013-69502020
<i>CCND1</i>	45	5 of 5	13.09	amplification	chr11:69412013-69502020
<i>CCND1</i>	6	5 of 5	2.75	amplification	chr11:69412013-69502020
<i>CCND1</i>	12	5 of 5	4.56	amplification	chr11:69412013-69502020
<i>CCND1</i>	19	5 of 5	4.69	amplification	chr11:69412013-69502020
<i>CCND1</i>	53	5 of 5	8.82	amplification	chr11:69412013-69502020
<i>CCND1</i>	12	5 of 5	4.47	amplification	chr11:69431286-69502020
<i>CCND1</i>	19	5 of 5	4.56	amplification	chr11:69412013-69502020
<i>CCND2</i>	8	5 of 5	2.03	amplification	chr12:4335813-4445571
<i>CCND3</i>	8	5 of 5	1.74	amplification	chr6:41853880-41956362
<i>CCNE1</i>	7	10 of 10	1.60	amplification	chr19:30253918-30349126
<i>CCNE1</i>	21	10 of 10	6.28	amplification	chr19:30276384-30360638
<i>CCNE1</i>	6	10 of 10	2.10	amplification	chr19:30253918-30360638
<i>CD274</i>	8	7 of 7	1.96	amplification	chr9:5456074-5470632
<i>CDK6</i>	9	7 of 7	2.41	amplification	chr7:92205279-92504369
<i>CDK8</i>	6	12 of 13	2.53	amplification	chr13:26911676-27021216
<i>CDKN2A</i>	0	5 of 5	0.79	loss	chr9:21968169-21994453
<i>CDKN2A</i>	0	5 of 5	0.43	loss	chr9:21853212-21998002

Gene	Copy number	CNA exons	CNA ratio	CNA type	CNA position
CDKN2A	0	5 of 5	0.40	loss	chr9:21853212-21998002
CDKN2A	0	5 of 5	0.35	loss	chr9:21853212-21998002
CDKN2A	0	5 of 5	0.13	loss	chr9:21853212-21998002
CDKN2A	0	5 of 5	0.45	loss	chr9:21968169-21994453
CDKN2A	0	5 of 5	0.20	loss	chr9:21853212-21998002
CDKN2A	0	4 of 5	0.21	loss	chr9:21853212-21981592
CDKN2B	0	5 of 5	0.79	loss	chr9:22002170-22010784
CDKN2B	0	5 of 5	0.13	loss	chr9:21998748-22101832
CDKN2B	0	5 of 5	0.43	loss	chr9:21998748-22101832
CDKN2B	0	5 of 5	0.20	loss	chr9:21998748-22101832
CDKN2B	0	5 of 5	0.49	loss	chr9:21998748-22101832
CDKN2B	0	5 of 5	0.35	loss	chr9:21998748-22101832
CSF3R	7	16 of 16	2.46	amplification	chr1:36931684-36945130
CTNNA1	0	4 of 17	0.23	loss	chr5:138221876-138253587
CUL4A	7	20 of 20	1.91	amplification	chr13:113863941-113917913
EMSY	6	20 of 20	1.62	amplification	chr11:76120008-76310898
EMSY	9	20 of 20	2.83	amplification	chr11:76113654-76310898
EMSY	10	20 of 20	4.03	amplification	chr11:76113654-76310898
EMSY	43	20 of 20	7.31	amplification	chr11:76113654-76310898
EMSY	17	20 of 20	5.46	amplification	chr11:76113654-76310898
EMSY	45	20 of 20	9.85	amplification	chr11:76113654-76310898
EMSY	9	20 of 20	2.23	amplification	chr11:76120008-76310898
EMSY	7	20 of 20	3.29	amplification	chr11:76113654-76310898
EMSY	6	20 of 20	2.46	amplification	chr11:76142889-76310898
EMSY	8	20 of 20	1.66	amplification	chr11:76113654-76310898
EPHB4	10	17 of 17	2.08	amplification	chr7:100401082-100424691
ERBB2	6	27 of 27	1.55	amplification	chr17:37807689-37933832
ERBB2	6	27 of 27	1.66	amplification	chr17:37807689-37933832
ERBB2	7	27 of 27	2.03	amplification	chr17:37807689-37933832
ERBB2	7	27 of 27	1.85	amplification	chr17:37807689-37933832
ESR1	23	8 of 8	8.82	amplification	chr6:152090577-152469340
FAS	0	10 of 10	0.49	loss	chr10:90750583-90775607
FGF12	8	6 of 6	2.73	amplification	chr3:191820777-192487207
FGF19	20	3 of 3	5.86	amplification	chr11:69514029-69561786
FGF19	8	3 of 3	3.03	amplification	chr11:69514029-69561786
FGF19	7	3 of 3	2.48	amplification	chr11:69514029-69561786
FGF19	32	3 of 3	4.66	amplification	chr11:69514029-69561786
FGF19	6	3 of 3	2.60	amplification	chr11:69514029-69561786
FGF19	11	3 of 3	2.10	amplification	chr11:69514029-69561786
FGF19	15	3 of 3	3.78	amplification	chr11:69514029-69561786
FGF19	16	3 of 3	2.51	amplification	chr11:69514029-69518644
FGF19	6	3 of 3	1.57	amplification	chr11:69514029-69561786
FGF19	10	3 of 3	3.58	amplification	chr11:69514029-69561786
FGF19	10	3 of 3	1.99	amplification	chr11:69514029-69561786
FGF19	9	3 of 3	2.85	amplification	chr11:69514029-69561786
FGF19	9	3 of 3	1.78	amplification	chr11:69514029-69561786
FGF19	13	3 of 3	3.18	amplification	chr11:69514029-69536217
FGF19	8	3 of 3	3.27	amplification	chr11:69514029-69561786
FGF19	6	3 of 3	2.41	amplification	chr11:69514029-69561786
FGF19	7	3 of 3	2.64	amplification	chr11:69514029-69561786

Gene	Copy number	CNA exons	CNA ratio	CNA type	CNA position
<i>FGF19</i>	7	3 of 3	1.60	amplification	chr11:69514029-69561786
<i>FGF19</i>	53	3 of 3	12.38	amplification	chr11:69514029-69561786
<i>FGF19</i>	13	3 of 3	5.24	amplification	chr11:69514029-69561786
<i>FGF19</i>	39	3 of 3	6.96	amplification	chr11:69514029-69561786
<i>FGF19</i>	41	3 of 3	11.71	amplification	chr11:69514029-69561786
<i>FGF23</i>	8	3 of 3	2.10	amplification	chr12:4462589-4488748
<i>FGF23</i>	14	3 of 3	2.13	amplification	chr12:4462589-4488748
<i>FGF3</i>	8	3 of 3	3.46	amplification	chr11:69580315-69683592
<i>FGF3</i>	6	3 of 3	2.28	amplification	chr11:69580315-69683592
<i>FGF3</i>	9	3 of 3	1.78	amplification	chr11:69580315-69683592
<i>FGF3</i>	12	3 of 3	4.96	amplification	chr11:69580315-69683592
<i>FGF3</i>	12	3 of 3	4.44	amplification	chr11:69580315-69683592
<i>FGF3</i>	7	3 of 3	1.83	amplification	chr11:69580315-69683592
<i>FGF3</i>	47	3 of 3	11.00	amplification	chr11:69580315-69633701
<i>FGF3</i>	39	3 of 3	6.96	amplification	chr11:69580315-69683592
<i>FGF3</i>	9	3 of 3	2.07	amplification	chr11:69614838-69683592
<i>FGF3</i>	8	3 of 3	1.51	amplification	chr11:69580315-69683592
<i>FGF3</i>	10	3 of 3	2.14	amplification	chr11:69580315-69683592
<i>FGF3</i>	15	3 of 3	3.34	amplification	chr11:69580315-69683592
<i>FGF3</i>	11	3 of 3	2.23	amplification	chr11:69580315-69683592
<i>FGF3</i>	40	3 of 3	11.39	amplification	chr11:69580315-69683592
<i>FGF3</i>	6	3 of 3	2.30	amplification	chr11:69625072-69683592
<i>FGF3</i>	9	3 of 3	2.46	amplification	chr11:69580315-69666638
<i>FGF3</i>	20	3 of 3	5.78	amplification	chr11:69580315-69683592
<i>FGF3</i>	7	3 of 3	2.48	amplification	chr11:69580315-69683592
<i>FGF3</i>	6	3 of 3	2.22	amplification	chr11:69580315-69683592
<i>FGF3</i>	7	3 of 3	1.62	amplification	chr11:69580315-69683592
<i>FGF3</i>	47	3 of 3	6.45	amplification	chr11:69580315-69683592
<i>FGF4</i>	20	3 of 3	5.66	amplification	chr11:69588076-69589852
<i>FGF4</i>	7	3 of 3	2.60	amplification	chr11:69588076-69589852
<i>FGF4</i>	8	3 of 3	1.48	amplification	chr11:69588076-69589852
<i>FGF4</i>	8	3 of 3	3.66	amplification	chr11:69588076-69589852
<i>FGF4</i>	7	3 of 3	1.83	amplification	chr11:69588076-69589852
<i>FGF4</i>	12	3 of 3	4.44	amplification	chr11:69588076-69589852
<i>FGF4</i>	47	3 of 3	6.50	amplification	chr11:69588076-69589852
<i>FGF4</i>	7	3 of 3	2.51	amplification	chr11:69588076-69589852
<i>FGF4</i>	15	3 of 3	3.23	amplification	chr11:69588076-69589852
<i>FGF4</i>	38	3 of 3	11.00	amplification	chr11:69588076-69589852
<i>FGF4</i>	6	3 of 3	1.57	amplification	chr11:69588076-69589852
<i>FGF4</i>	9	3 of 3	2.64	amplification	chr11:69588076-69589852
<i>FGF4</i>	11	3 of 3	2.85	amplification	chr11:69588076-69589852
<i>FGF4</i>	10	3 of 3	2.35	amplification	chr11:69588076-69589852
<i>FGF4</i>	8	3 of 3	3.14	amplification	chr11:69588076-69589852
<i>FGF4</i>	6	3 of 3	2.10	amplification	chr11:69588076-69589852
<i>FGF4</i>	11	3 of 3	4.56	amplification	chr11:69588076-69589852
<i>FGF4</i>	44	3 of 3	10.27	amplification	chr11:69588076-69589852
<i>FGF4</i>	42	3 of 3	7.46	amplification	chr11:69588076-69589852
<i>FGF4</i>	6	3 of 3	2.39	amplification	chr11:69588076-69589852
<i>FGF4</i>	9	3 of 3	1.92	amplification	chr11:69588076-69589852
<i>FGF6</i>	8	3 of 3	2.04	amplification	chr12:4494593-4598143

Gene	Copy number	CNA exons	CNA ratio	CNA type	CNA position
<i>FGF6</i>	14	3 of 3	2.03	amplification	chr12:4494593-4593430
<i>FGFR1</i>	12	18 of 18	3.07	amplification	chr8:38271145-38322355
<i>FGFR1</i>	89	18 of 18	14.93	amplification	chr8:38226104-38363070
<i>FGFR1</i>	7	18 of 18	1.83	amplification	chr8:38231865-38363070
<i>FGFR1</i>	17	18 of 18	3.39	amplification	chr8:38226104-38363070
<i>FGFR1</i>	9	18 of 18	3.27	amplification	chr8:38226104-38363070
<i>FGFR1</i>	25	18 of 18	5.70	amplification	chr8:38226104-38363070
<i>FGFR1</i>	36	18 of 18	9.92	amplification	chr8:38226104-38363070
<i>FGFR1</i>	34	18 of 18	4.86	amplification	chr8:38226104-38363070
<i>FGFR1</i>	8	18 of 18	3.05	amplification	chr8:38271145-38363070
<i>FGFR1</i>	6	18 of 18	2.06	amplification	chr8:38226104-38363070
<i>FGFR1</i>	9	18 of 18	2.28	amplification	chr8:38271145-38363070
<i>FGFR1</i>	11	18 of 18	1.45	amplification	chr8:38271145-38363070
<i>FGFR1</i>	15	18 of 18	2.28	amplification	chr8:38226104-38363070
<i>FGFR1</i>	17	18 of 18	2.83	amplification	chr8:38259351-38363070
<i>FGFR1</i>	8	18 of 18	2.14	amplification	chr8:38231865-38363070
<i>FGFR1</i>	16	18 of 18	4.29	amplification	chr8:38226104-38363070
<i>FGFR4</i>	6	16 of 16	2.66	amplification	chr5:176449475-176569318
<i>FGFR4</i>	8	16 of 16	2.23	amplification	chr5:176449475-176569318
<i>GNAS</i>	11	15 of 15	4.32	amplification	chr20:57415161-57485884
<i>GNAS</i>	7	15 of 15	2.36	amplification	chr20:57415161-57485884
<i>GNAS</i>	6	13 of 15	2.41	amplification	chr20:57466781-57485884
<i>GNAS</i>	7	13 of 15	2.17	amplification	chr20:57466781-57485884
<i>HGF</i>	7	19 of 19	1.83	amplification	chr7:81331896-81399308
<i>HGF</i>	11	19 of 19	2.51	amplification	chr7:81287783-81435614
<i>HRAS</i>	9	5 of 5	2.41	amplification	chr11:511507-584252
<i>IGF1R</i>	13	20 of 21	3.73	amplification	chr15:99192792-99491937
<i>IKBKE</i>	58	20 of 20	13.55	amplification	chr1:206646549-206669525
<i>IKBKE</i>	8	20 of 20	1.77	amplification	chr1:206646549-206669525
<i>IRS2</i>	15	5 of 5	4.14	amplification	chr13:110406186-110438400
<i>IRS2</i>	75	5 of 5	17.51	amplification	chr13:110406186-110438400
<i>JAK2</i>	8	23 of 23	2.08	amplification	chr9:5021987-5126801
<i>JUN</i>	7	3 of 3	2.91	amplification	chr1:59219094-59298520
<i>KDM5A</i>	11	28 of 28	3.56	amplification	chr12:394621-498257
<i>KDM5A</i>	8	28 of 28	2.17	amplification	chr12:394621-498257
<i>KDM5A</i>	8	28 of 28	2.08	amplification	chr12:394621-498257
<i>KDM5A</i>	7	28 of 28	2.91	amplification	chr12:394621-498257
<i>KRAS</i>	8	5 of 5	1.88	amplification	chr12:25344730-25417157
<i>KRAS</i>	8	5 of 5	2.06	amplification	chr12:25344730-25448217
<i>LYN</i>	9	12 of 12	2.60	amplification	chr8:56854418-56922669
<i>LYN</i>	8	12 of 12	1.96	amplification	chr8:56854418-56922669
<i>LYN</i>	10	12 of 12	1.89	amplification	chr8:56854418-56922669
<i>LYN</i>	11	12 of 12	2.75	amplification	chr8:56854418-56922669
<i>LYN</i>	7	12 of 12	2.06	amplification	chr8:56854418-56922669
<i>LYN</i>	10	12 of 12	2.20	amplification	chr8:56854418-56922669
<i>MAP2K1</i>	7	11 of 11	1.99	amplification	chr15:66679660-66782960
<i>MAP2K4</i>	0	12 of 12	0.49	loss	chr17:11835312-12105692
<i>MAP2K4</i>	0	8 of 12	0.18	loss	chr17:11835312-12016677
<i>MAP2K4</i>	0	10 of 12	0.41	loss	chr17:11958192-12105692
<i>MAP2K4</i>	0	4 of 12	0.21	loss	chr17:12028584-12105692

Gene	Copy number	CNA exons	CNA ratio	CNA type	CNA position
MAP2K4	0	8 of 12	0.47	loss	chr17:11995871-12105692
MAP2K4	0	5 of 12	0.40	loss	chr17:11835312-12006910
MAP2K4	0	12 of 12	0.32	loss	chr17:11835312-12105692
MCL1	8	5 of 5	2.95	amplification	chr1:150518281-150600810
MCL1	7	5 of 5	2.46	amplification	chr1:150511135-150600810
MCL1	8	5 of 5	2.08	amplification	chr1:150511135-150552548
MCL1	7	5 of 5	2.55	amplification	chr1:150511135-150600810
MDM2	10	11 of 11	2.33	amplification	chr12:69153996-69277205
MDM2	12	11 of 11	3.73	amplification	chr12:69153996-69277205
MDM2	26	11 of 11	6.23	amplification	chr12:69153996-69277205
MDM2	6	11 of 11	2.17	amplification	chr12:69202199-69277205
MDM4	8	10 of 10	1.84	amplification	chr1:204494620-204518810
MDM4	7	8 of 10	1.95	amplification	chr1:204494620-204513812
MDM4	7	10 of 10	2.10	amplification	chr1:204494620-204518810
MDM4	8	10 of 10	2.07	amplification	chr1:204494620-204518810
MDM4	8	9 of 10	1.87	amplification	chr1:204495460-204518810
MTAP	0	7 of 8	0.39	loss	chr9:21815410-21862058
MTAP	0	7 of 8	0.77	loss	chr9:21815410-21862058
MTAP	0	8 of 8	0.18	loss	chr9:21802699-21862058
MTAP	0	8 of 8	0.13	loss	chr9:21802699-21862058
MTAP	0	4 of 8	0.22	loss	chr9:21837893-21862058
MTAP	0	8 of 8	0.42	loss	chr9:21802699-21862058
MTAP	0	8 of 8	0.36	loss	chr9:21802699-21862058
MTAP	0	7 of 8	0.57	loss	chr9:21815410-21862058
MYC	11	5 of 5	4.59	amplification	chr8:128706589-128801451
MYC	19	5 of 5	4.59	amplification	chr8:128706589-128801451
MYC	8	5 of 5	2.00	amplification	chr8:128719852-128801451
MYC	8	5 of 5	2.35	amplification	chr8:128742842-128772066
MYC	8	5 of 5	2.20	amplification	chr8:128706589-128801451
MYC	7	5 of 5	2.46	amplification	chr8:128706589-128801451
MYC	39	5 of 5	10.78	amplification	chr8:128706589-128801451
MYC	7	5 of 5	1.59	amplification	chr8:128706589-128801451
MYC	13	5 of 5	4.03	amplification	chr8:128706589-128801451
MYC	8	5 of 5	2.58	amplification	chr8:128706589-128772066
MYC	7	5 of 5	3.16	amplification	chr8:128706589-128801451
MYC	15	5 of 5	2.97	amplification	chr8:128706589-128801451
MYC	8	5 of 5	1.69	amplification	chr8:128706589-128801451
MYC	7	5 of 5	2.08	amplification	chr8:128727876-128753204
MYC	8	5 of 5	2.43	amplification	chr8:128706589-128780331
MYC	7	4 of 5	1.87	amplification	chr8:128706589-128751994
MYC	6	5 of 5	1.71	amplification	chr8:128706589-128801451
MYC	14	5 of 5	3.14	amplification	chr8:128706589-128772066
MYCL1	14	5 of 5	5.78	amplification	chr1:40360900-40368610
NF1	0	36 of 59	0.26	loss	chr17:29422292-29596265
NFKBIA	7	6 of 6	2.85	amplification	chr14:35871177-35873850
NOTCH3	7	33 of 33	1.68	amplification	chr19:15271472-15311722
PARP1	9	23 of 23	2.35	amplification	chr1:226549136-226595635
PDCD1LG2	8	6 of 6	1.75	amplification	chr9:5522509-5570021
PIK3C2B	7	32 of 32	2.60	amplification	chr1:204393979-204429102
PIK3C2B	7	32 of 32	2.30	amplification	chr1:204393979-204438930

Gene	Copy number	CNA exons	CNA ratio	CNA type	CNA position
<i>PIK3C2B</i>	8	32 of 32	2.16	amplification	chr1:204393979-204438930
<i>PIK3C2B</i>	8	32 of 32	1.80	amplification	chr1:204393979-204438930
<i>PIK3C2B</i>	8	26 of 32	2.46	amplification	chr1:204393979-204429102
<i>PIK3C2B</i>	11	32 of 32	2.31	amplification	chr1:204393979-204438930
<i>PIK3C2B</i>	7	32 of 32	1.85	amplification	chr1:204393979-204438930
<i>PIK3CA</i>	55	20 of 20	12.82	amplification	chr3:178875270-178996445
<i>PIK3CA</i>	7	20 of 20	1.61	amplification	chr3:178875270-178969237
<i>PRKCI</i>	7	18 of 18	1.66	amplification	chr3:169940443-170020936
<i>PTEN</i>	0	9 of 9	0.49	loss	chr10:89548329-89795653
<i>PTEN</i>	0	9 of 9	0.54	loss	chr10:89548329-89795653
<i>PTEN</i>	0	9 of 9	0.34	loss	chr10:89599345-89725229
<i>PTEN</i>	0	9 of 9	0.30	loss	chr10:89548329-89764620
<i>PTEN</i>	0	1 of 9	0.23	loss	chr10:89653759-89653888
<i>RAD21</i>	11	13 of 13	2.16	amplification	chr8:117859738-117878968
<i>RAD21</i>	11	13 of 13	2.89	amplification	chr8:117859738-117878968
<i>RAD21</i>	10	13 of 13	3.01	amplification	chr8:117859738-117878968
<i>RAD21</i>	8	13 of 13	2.30	amplification	chr8:117859738-117878968
<i>RAD21</i>	8	13 of 13	2.38	amplification	chr8:117859738-117878968
<i>RAD21</i>	9	13 of 13	4.44	amplification	chr8:117859738-117878968
<i>RAD21</i>	8	13 of 13	2.85	amplification	chr8:117859738-117878968
<i>RAD21</i>	9	13 of 13	2.41	amplification	chr8:117859738-117878968
<i>RAD21</i>	7	13 of 13	1.93	amplification	chr8:117859738-117878968
<i>RAD21</i>	15	13 of 13	4.38	amplification	chr8:117859738-117878968
<i>RAD21</i>	16	13 of 13	6.82	amplification	chr8:117859738-117878968
<i>RAD21</i>	8	13 of 13	1.84	amplification	chr8:117859738-117878968
<i>RAD21</i>	7	13 of 13	2.46	amplification	chr8:117859738-117878968
<i>RAD21</i>	7	13 of 13	1.93	amplification	chr8:117859738-117878968
<i>RAD21</i>	11	13 of 13	3.16	amplification	chr8:117859738-117878968
<i>RAD21</i>	10	13 of 13	2.58	amplification	chr8:117859738-117878968
<i>RAD21</i>	11	12 of 13	1.97	amplification	chr8:117861161-117878968
<i>RAD21</i>	13	13 of 13	2.97	amplification	chr8:117859738-117878968
<i>RAD21</i>	8	13 of 13	2.11	amplification	chr8:117859738-117878968
<i>RAD21</i>	9	13 of 13	2.75	amplification	chr8:117859738-117878968
<i>RAD21</i>	9	13 of 13	2.81	amplification	chr8:117859738-117878968
<i>RAD21</i>	26	13 of 13	10.13	amplification	chr8:117859738-117878968
<i>RAD21</i>	9	13 of 13	1.80	amplification	chr8:117859738-117878968
<i>RAF1</i>	8	16 of 16	2.33	amplification	chr3:12576837-12709494
<i>RB1</i>	0	6 of 27	0.60	loss	chr13:48947519-48972066
<i>RICTOR</i>	6	39 of 39	2.22	amplification	chr5:38942378-39074519
<i>RICTOR</i>	8	39 of 39	2.10	amplification	chr5:38942378-39074519
<i>ROS1</i>	8	43 of 43	3.29	amplification	chr6:117609654-117746822
<i>STK11</i>	0	8 of 9	0.24	loss	chr19:1120199-1223171
<i>TBX3</i>	0	8 of 8	0.20	loss	chr12:115109645-115121005
<i>TERC</i>	7	3 of 3	2.45	amplification	chr3:169482000-169483150
<i>TERC</i>	7	3 of 3	2.04	amplification	chr3:169482000-169483150
<i>TP53</i>	0	14 of 14	0.12	loss	chr17:7537783-7580715
<i>VEGFA</i>	8	8 of 8	2.71	amplification	chr6:43738443-43752419
<i>VEGFA</i>	8	8 of 8	1.62	amplification	chr6:43738443-43752419
<i>WHSC1L1</i>	14	23 of 23	3.73	amplification	chr8:38133159-38205689
<i>WHSC1L1</i>	8	23 of 23	1.77	amplification	chr8:38133159-38205689

Gene	Copy number	CNA exons	CNA ratio	CNA type	CNA position
WHSC1L1	9	23 of 23	3.66	amplification	chr8:38133159-38205689
WHSC1L1	9	23 of 23	2.17	amplification	chr8:38133159-38205689
WHSC1L1	110	23 of 23	18.51	amplification	chr8:38133159-38205689
WHSC1L1	19	23 of 23	4.59	amplification	chr8:38133159-38205689
WHSC1L1	15	23 of 23	2.79	amplification	chr8:38133159-38205689
WHSC1L1	6	23 of 23	2.36	amplification	chr8:38133159-38205689
WHSC1L1	21	23 of 23	4.44	amplification	chr8:38133159-38205689
WHSC1L1	45	23 of 23	11.63	amplification	chr8:38133159-38205689
WHSC1L1	16	23 of 23	1.99	amplification	chr8:38133159-38205689
WHSC1L1	25	23 of 23	6.96	amplification	chr8:38133159-38205689
WHSC1L1	10	23 of 23	3.81	amplification	chr8:38133159-38205689
WHSC1L1	10	23 of 23	2.62	amplification	chr8:38133159-38205689
WHSC1L1	45	23 of 23	5.98	amplification	chr8:38133159-38205689
WHSC1L1	21	23 of 23	3.41	amplification	chr8:38133159-38205689
WHSC1L1	33	23 of 23	7.36	amplification	chr8:38133159-38205689
ZNF217	7	4 of 4	2.03	amplification	chr20:52188273-52199365
ZNF217	16	4 of 4	4.32	amplification	chr20:52188273-52199365
ZNF217	18	4 of 4	7.36	amplification	chr20:52188273-52199365
ZNF217	8	4 of 4	4.14	amplification	chr20:52188273-52199365
ZNF217	6	4 of 4	2.71	amplification	chr20:52188273-52199365
ZNF703	6	2 of 2	2.33	amplification	chr8:37553497-37556192
ZNF703	15	2 of 2	2.55	amplification	chr8:37553497-37556192
ZNF703	129	2 of 2	21.86	amplification	chr8:37553497-37556192
ZNF703	20	2 of 2	4.96	amplification	chr8:37553497-37556192
ZNF703	9	2 of 2	4.92	amplification	chr8:37553497-37556192
ZNF703	14	2 of 2	3.68	amplification	chr8:37553497-37556192
ZNF703	26	2 of 2	6.11	amplification	chr8:37553497-37556192
ZNF703	8	2 of 2	2.13	amplification	chr8:37553497-37556192
ZNF703	42	2 of 2	11.47	amplification	chr8:37553497-37556192
ZNF703	9	2 of 2	2.53	amplification	chr8:37553497-37556192
ZNF703	15	2 of 2	5.43	amplification	chr8:37553497-37556192
ZNF703	30	2 of 2	8.51	amplification	chr8:37553497-37556192
ZNF703	14	2 of 2	3.01	amplification	chr8:37553497-37556192
ZNF703	15	2 of 2	6.06	amplification	chr8:37553497-37556192
ZNF703	27	2 of 2	3.97	amplification	chr8:37553497-37556192
ZNF703	27	2 of 2	5.82	amplification	chr8:37553497-37556192

Supplementary Table 8: List of all rearrangements from the somatic genotyping (N=94) [N/A: not applicable]

Gene 1	Gene 2	Rearrangement position 1	Rearrangement position 2
<i>BRAF</i>	N/A	chr7:140486583-140486699	chr7:139116608-139116734
<i>TP53</i>	<i>TP53</i>	chr17:7578183-7578433	chr17:7574147-7574262
<i>BRIP1</i>	N/A	chr17:59876577-59876803	chr17:59748563-59748968
<i>NF1</i>	<i>RAD23B</i>	chr17:29541541-29541743	chr9:110050850-110050993
<i>FAM123B</i>	N/A	chrX:63412747-63412867	chrX:63386047-63386285
<i>APC</i>	<i>EFCAB7</i>	chr5:112154644-112154920	chr1:64009672-64009843
<i>KDM5C</i>	N/A	chrX:53228051-53228203	chr5:1115976-1116248
<i>EZH2</i>	<i>CUL1</i>	chr7:148507454-148507658	chr7:148453200-148453394
<i>NF1</i>	<i>LAD1</i>	chr17:29482871-29483024	chr1:201355635-201355971
<i>RB1</i>	<i>RB1</i>	chr13:48942615-48942884	chr13:48957136-48957380
<i>TNFRSF14</i>	N/A	chr1:2491981-2492192	chr1:2438306-2438469
<i>BRAF</i>	N/A	chr7:140487094-140487355	chr7:140427718-140428130
<i>BRIP1</i>	N/A	chr17:59793179-59793451	chr17:56119950-56120291
<i>NOTCH2</i>	<i>DR1</i>	chr1:120465170-120465418	chr1:93818791-93819344
<i>MYB</i>	N/A	chr6:135527962-135528410	chr6:135568285-135568731
<i>PTEN</i>	<i>PTEN</i>	chr10:89711727-89711960	chr10:89679375-89679746
<i>ETV6</i>	N/A	chr12:12031262-12031542	chr12:12201782-12202021
<i>NOTCH2</i>	<i>SRCAP</i>	chr1:120464714-120464993	chr16:30710944-30711255
<i>APC</i>	N/A	chr5:112173653-112173871	chr14:91992638-91992980
<i>FUBP1</i>	N/A	chr1:78430609-78430804	chrX:135015488-135015680
<i>SMARCA4</i>	<i>ASNA1</i>	chr19:11134046-11134237	chr19:12852577-12852786
<i>NBN</i>	<i>XKR4</i>	chr8:90990392-90990636	chr8:56088404-56088587
<i>CDH1</i>	<i>CDH1</i>	chr16:68843969-68844194	chr16:68833685-68833854

Supplementary Table 9: Categorization of genes in the 26-gene testing panel

No	Gene Name	BRCA1/2	Other Homologous Recombination (HRR) Genes	Other DNA Repair Genes	Other BC Risk Genes
1	<i>APC</i>				X
2	<i>ATM</i>		X		
3	<i>BARD1</i>		X		
4	<i>BRCA1</i>	X			
5	<i>BRCA2</i>	X			
6	<i>BRIP1</i>			X	
7	<i>CDH1</i>				X
8	<i>CDKN2A</i>				X
9	<i>CHEK2</i>			X	
10	<i>FANCC</i>		X		
11	<i>KRAS</i>				X
12	<i>MEN1</i>				X
13	<i>MLH1</i>			X	
14	<i>MRE11A</i>			X	
15	<i>MSH2</i>			X	
16	<i>MSH6</i>			X	
17	<i>MUTHY</i>			X	
18	<i>NBN</i>			X	
19	<i>NF1</i>				X
20	<i>PALB2</i>		X		
21	<i>PMS2</i>			X	
22	<i>PTEN</i>				X
23	<i>RAD51C</i>		X		
24	<i>RAD51D</i>		X		
25	<i>TP53</i>				X
26	<i>XRCC2</i>		X		

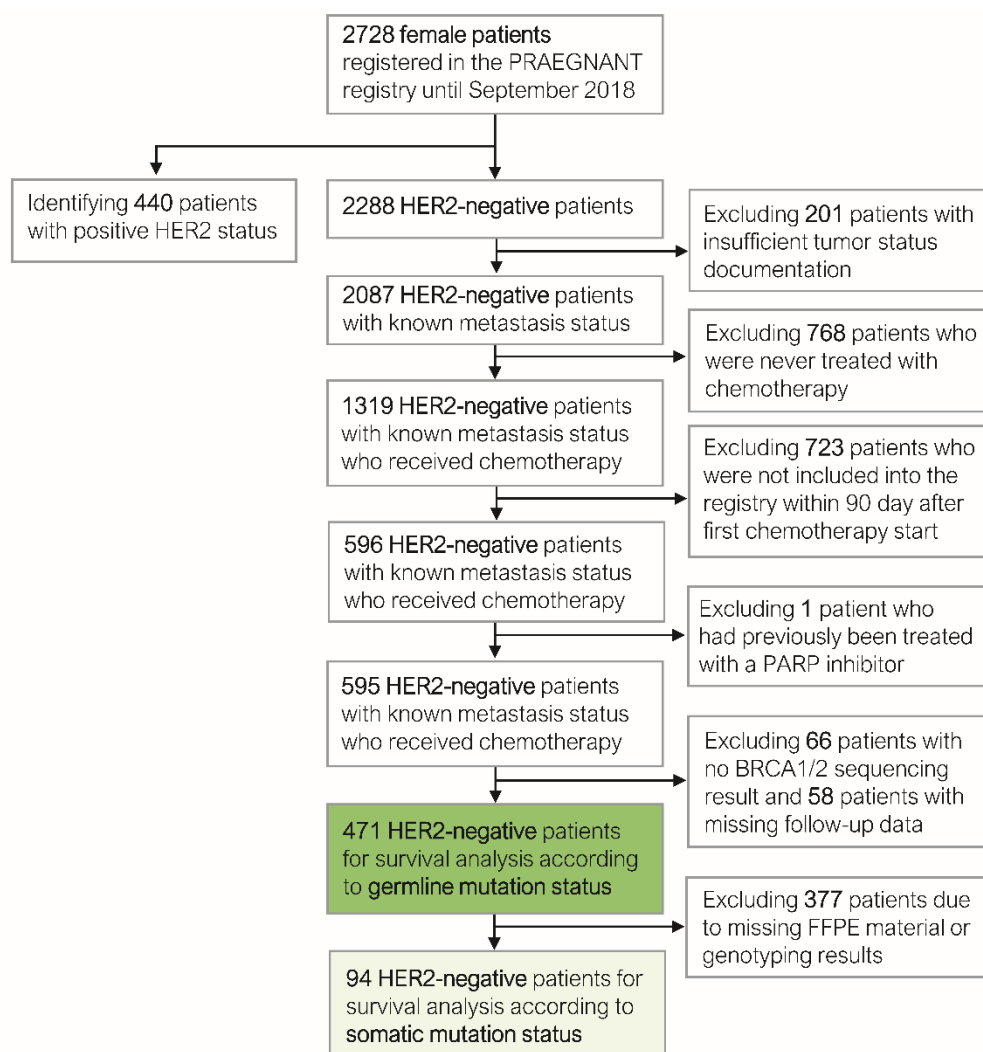
Supplementary Table 10: Data categories captured in the PRAEGNANT study [ECOG: Eastern Cooperative Oncology Group - performance status; PRO: patient-reported outcome]

Data continuously captured if applicable	Data assessed at study entry	Data assessed at follow-up care appointments
Concomitant diseases	Life status, ECOG	Life status, ECOG
Concomitant medication	Quality of life	Quality of life
Cancer systemic therapies	Breast cancer risk factor questionnaire	Breast and axilla evaluation
Cancer radiotherapy	Breast and axilla evaluation	Distant metastasis evaluation
Cancer surgery	Distant metastasis evaluation	Biomaterial ascertainment
Breast cancer right side	Biomaterial ascertainment	PRO questionnaires
Breast cancer left side	PRO questionnaires	

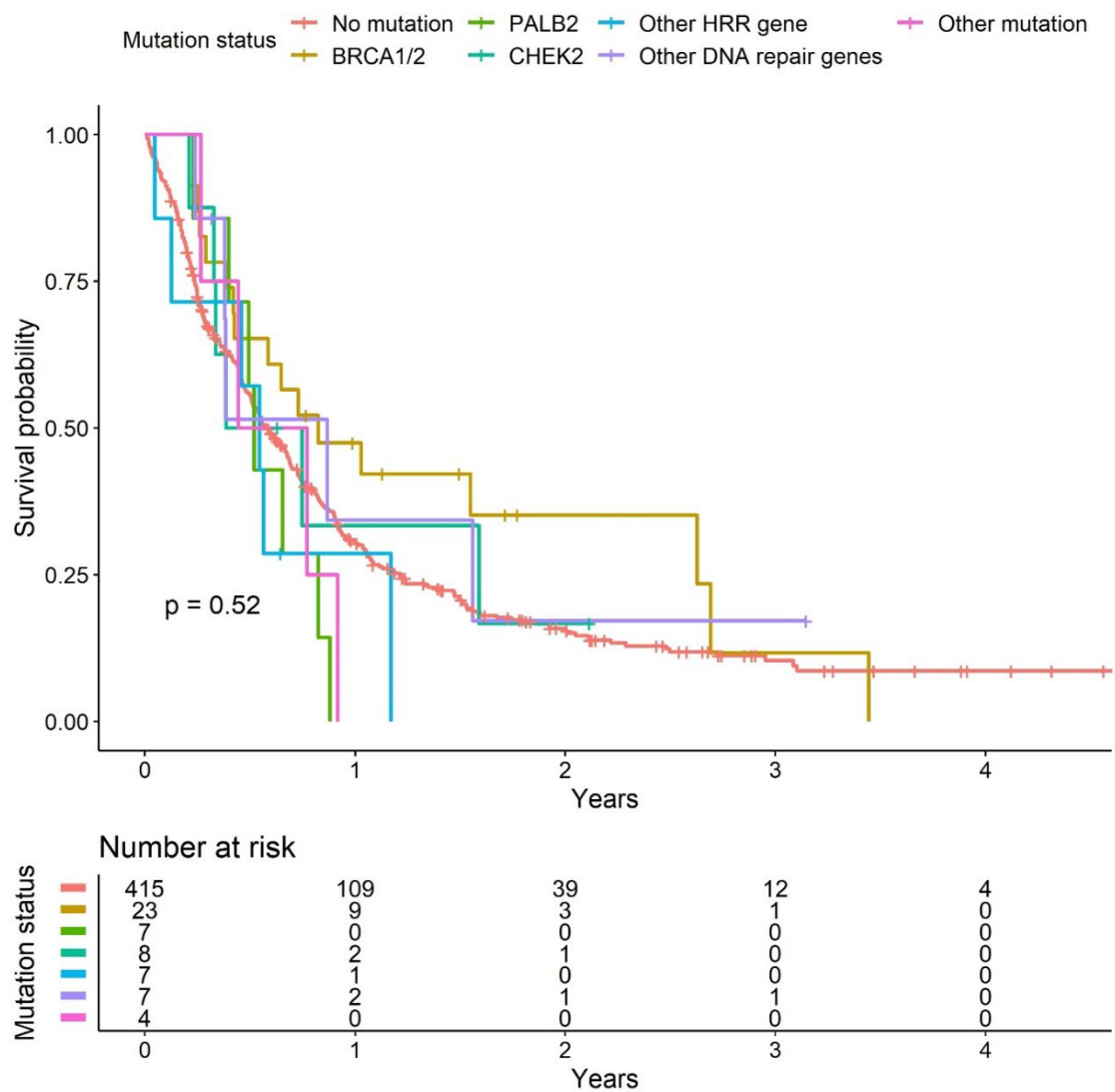
Supplementary Table 11: List of genes included in the QIaseq panel

HGNC symbol	Reference Sequence	Ensemble Transcript Id	Chromosome	Start position	End position	strand	Ensemble gene id
APC	NM000038.5	ENST00000257430	5	112043195	112181936	1	ENSG00000134982
ATM	NM000051.3	ENST00000278616	11	108093211	108239829	1	ENSG00000149311
BARD1	NM000465.3	ENST00000260947	2	215590370	215674428	-1	ENSG00000138376
BRCA1	NM007294.3	ENST00000357654	17	41196312	41277500	-1	ENSG00000012048
BRCA2	NM000059.3	ENST00000544455	13	32889611	32973805	1	ENSG00000139618
BRIP1	NM032043.2	ENST00000259008	17	59758627	59940882	-1	ENSG00000136492
CDH1	NM004360.4	ENST00000261769	16	68771128	68869451	1	ENSG00000039068
CDKN2A	NM000077.4	ENST00000304494	9	21967751	21995300	-1	ENSG00000147889
CHEK2	NM007194.3	ENST00000328354	22	29083731	29138410	-1	ENSG00000183765
FANCC	NM000136.2	ENST00000289081	9	97861336	98079991	-1	ENSG00000158169
KRAS	NM004985.4	ENST00000311936	12	25357723	25403870	-1	ENSG00000133703
MEN1	NM130799.2	ENST00000312049	11	64570982	64578766	-1	ENSG00000133895
MLH1	NM000249.3	ENST00000231790	3	37034823	37107380	1	ENSG00000076242
MRE11A	NM005591.3	ENST00000323929	11	94152895	94227074	-1	ENSG00000020922
MSH2	NM000251.2	ENST00000233146	2	47630108	47789450	1	ENSG00000095002
MSH6	NM000179.2	ENST00000234420	2	47922669	48037240	1	ENSG00000116062
MUTYH	NM001128425.1	ENST00000450313	1	45794835	45806142	-1	ENSG00000132781
NBN	NM002485.4	ENST00000265433	8	90945564	91015456	-1	ENSG00000104320
NF1	NM001042492.2	ENST00000358273	17	29421945	29709134	1	ENSG00000196712
PALB2	NM024675.3	ENST00000261584	16	23614488	23652631	-1	ENSG00000083093
PMS2	NM000535.6	ENST00000265849	7	6012870	6048756	-1	ENSG00000122512
PTEN	NM000314.6	ENST00000371953	10	89622870	89731687	1	ENSG00000171862
RAD51C	NM058216.2	ENST00000337432	17	56769934	56811703	1	ENSG00000108384
RAD51D	NM001142571	ENST00000345365	17	33426811	33448541	-1	ENSG00000185379
TP53	NM000546.5	ENST00000269305	17	7565097	7590856	-1	ENSG00000141510
XRCC2	NM005431.1	ENST00000359321	7	152341864	152373250	-1	ENSG00000196584

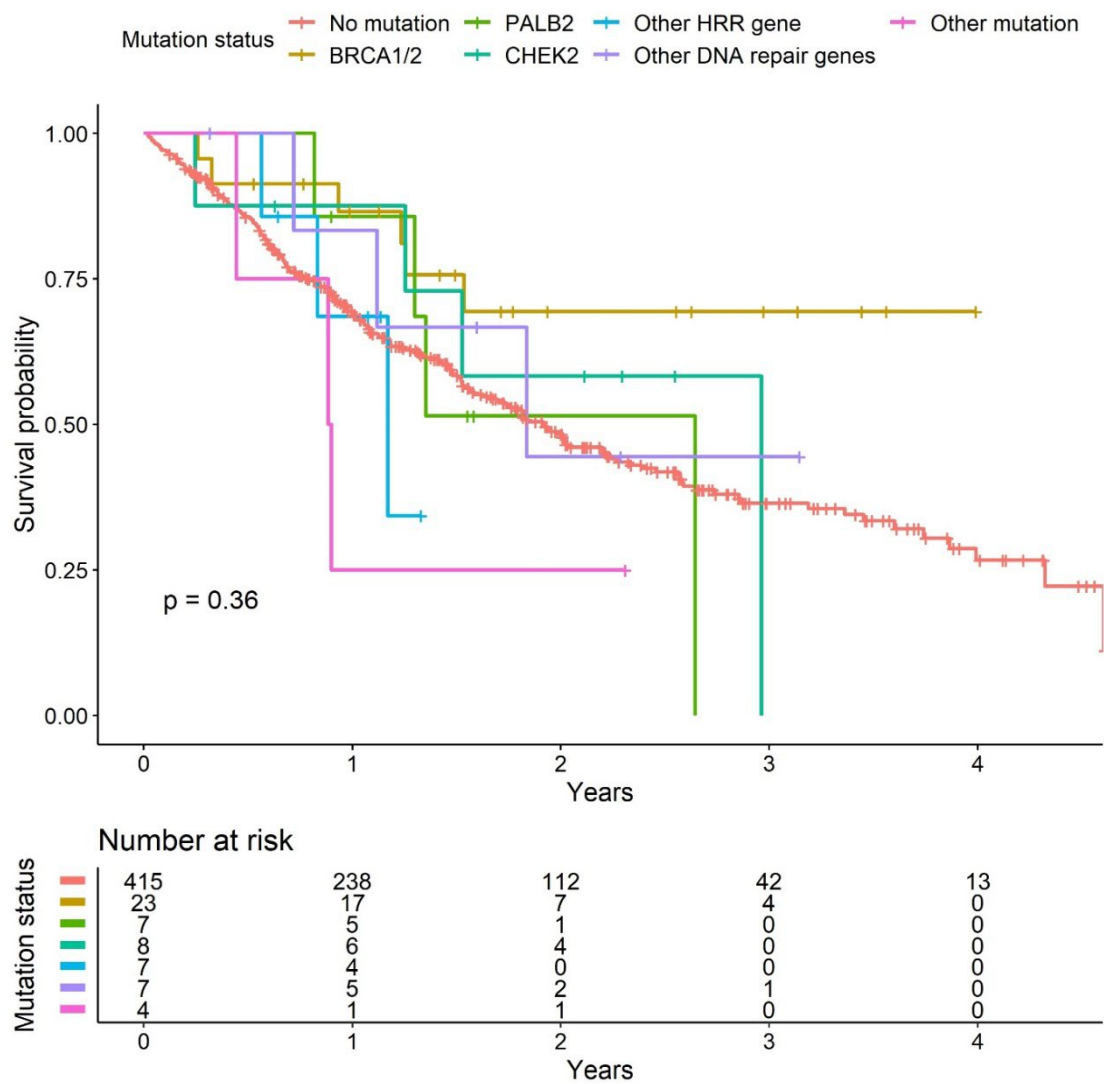
Supplementary Figures



Supplementary Figure 1: Patient Flow Chart



Supplementary Figure 2: Kaplan-Meier curves for progression free survival according to mutation status (7 groups)



Supplementary Figure 3: Kaplan-Meier curves for overall survival according to mutation status (7 groups)